INFORMATION FOR THE PUBLIC

University of Antwerp

A Phase 2, double-blind, randomized, placebo-controlled, multicenter study to evaluate the safety and immunogenicity of two novel live attenuated serotype 2 oral poliovirus vaccines candidates, in healthy adults and adolescents previously vaccinated with oral polio vaccine (OPV) or inactivated polio vaccine (IPV), compared with historical controls given Sabin OPV2 or placebo.

European notification number
[B/BE/18/BVW2]

The release of genetically modified organisms (GMOs) in the environment is strictly regulated at European level by directive 2001/18/EC of 12 March 2001 repealing directive 90/220/EEC and at Belgian level by a new Royal Decree "regulating the deliberate release and/or marketing of GMOs or products that contain GMOs into the environment" repealing the Royal Decree of 18 December 1998. The transposition procedure is still ongoing for the moment.

To ensure the safe use of GMOs, the provisions of the Royal Decree above stipulate that the release of GMOs for experimental aims is prohibited without prior consent from the competent Minister. The decision is based on a thorough evaluation of the biosafety of the planned release, which is conducted by the Biosafety Advisory Council, composed of different Scientific Committees grouping independent experts from Belgian universities and governmental institutes.

To acquire the necessary authorization from the competent Minister, the research centre University of Antwerp submitted an application dossier to the competent authority. On the basis of the advice of the Biosafety Council, the competent minister could grant a permission to the research centre University of Antwerp to conduct experiments with two candidate novel Oral Poliomyelitis Vaccines, Type 2, as stipulated in the application B/BE/18/BVW2.

The release will take place at 2 experimental locations in Flanders in the municipality(ies) of the Antwerp University, campus Drie Eiken, and Ghent University Hospital. It is expected to start on Q3/Q4 2018 and to be completed in Q2 2019.

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GENERAL INFORMATION:

DESCRIPTION OF THE GENETICALLY MODIFIED MICRO-ORGANISM (GMM)

Introduction

Poliomyelitis (also referred to as polio) is a highly contagious viral disease caused by one of the three types of the polio virus. Infections can result in life-long paralysis and, in some cases, death. Most infections with the polio virus are not accompanied by any symptoms, and only one in 200–300 infected individuals will develop the severely paralyzing form of the disease. Individuals infected with polio will continue to eliminate the polio virus in their stool for several weeks; this is known as ‘shedding’. Polio is primarily transmitted through the ingestion (through the mouth) of food and water contaminated with polio-positive fecal particles. This is referred to as feco-oral transmission. It can also be transmitted through saliva.

Polio can be prevented effectively through the administration of a polio vaccine. Worldwide polio vaccination campaigns have been highly successful, having reduced the number of cases of polio by 99.9% since 1988. The wild Type 2 has been fully eliminated. Type 1 is currently circulating in three countries: Afghanistan, Pakistan and Nigeria.

The most recent case of polio in Belgium was documented in 1999. In 2002, The World Health Organization (WHO) declared the European region free of polio, owing to the efficient vaccination campaigns. All preparations are currently being made to eliminate polio throughout the world. The current trial fits within this elimination plan.

There are two types of polio vaccines: the inactivated polio vaccine (IPV), which is administered by intramuscular (in the muscle) injection, and the oral, live attenuated polio vaccine (Sabin OPV), which is administered as drops in the mouth.

The attenuated virus in Sabin OPV can undergo certain changes in the intestines of the vaccinated individual, which can cause the virus to emerge in a stronger form. These changed or mutated viruses can cause severe paralysis in the vaccinated individuals and possibly in non-vaccinated individuals with whom they come into contact. This paralysis, known as vaccine-associated paralytic polio (VAPP), occurs in 4.7 of every 1 million infants who receive Sabin OPV, usually after the administration of the first dose (Alexander et al., 2004).

In recent decades, all countries in the EU have shifted from Sabin OPV to IPV in order to avoid the risk of vaccine-associated paralytic polio. In Belgium, the oral polio vaccine was used until 2000. Until early 2016, the trivalent OPV, which contains polio virus Types 1, 2 and 3 (Sabin tOPV), was used in most developing countries, as it worked well, and was easy and inexpensive to administer. Sabin tOPV was also highly effective in interrupting the spread of the virus in case of an epidemic.

Within the framework of the worldwide elimination of polio, each country will eventually shift from a Sabin OPV vaccination program to an IPV vaccination program, although this will take several more years and will be accomplished in steps.

As an initial step, a worldwide shift (more specifically, in more than 150 developing countries) was made in April 2016 from Sabin tOPV (containing Types 1, 2 and 3) to a bivalent OPV, containing only Types 1 and 3, (Sabin bOPV). The wild Type 2 polio virus has not been in circulation for nearly 20 years; the last case was identified in 1999. Nevertheless, Type 2 polio virus from the vaccine has been primarily responsible for the circulation of mutated strains. The shift from tOPV to bOPV and to IPV will thus reduce the risk of polio caused by mutated vaccine strains. Only Sabin OPV vaccines containing Types 1 and 3 are now routinely used in these countries. The WHO has access to a supply of Sabin OPV2, because in some parts of the world vaccine derived Type 2 polio virus is circulating and has caused outbreaks of disease. An example of this is happening in Syria, where WHO has begun a vaccination campaign because of an outbreak of vaccine derived poliovirus.

To address these outbreaks of polio that have resulted from mutations in Sabin OPV2, two novel OPV2 (nOPV2) candidate vaccines are being developed which are designed to be less likely to mutate to a form that can cause VAPP.

Description of GMM

The nOPV2 candidate vaccines are derived from Sabin OPV2 which has been used as part of tOPV vaccination programs until April 2016. Sabin OPV2 contains an attenuated or weakened strain of poliovirus. The nOPV2 candidate vaccines have changes in their genome that are intended to make them more stable than Sabin OPV2. They are designed to be less likely to change after administration to humans and therefore, less likely to cause VAPP. Whereas

attenuation of Sabin OPV2 is based on two single nucleotide mutations, each of the two nOPV2 candidate vaccines contain more changes to the genetic sequence which reduces the possibility of the viruses changing to a dangerous form when replicating in the intestines. These changes to the sequence do not involve incorporating genetic information from other organisms. The changes also do not induce the expression of new functions.

TYPE AND PURPOSE OF THE ENVISAGED TRIAL

The proposed trial will evaluate how 332 healthy volunteers, aged 15 to 50 years, will respond when they receive one of the two novel candidate vaccines. Volunteers will be selected that have already been vaccinated against polio in their past: two hundred volunteers will have been vaccinated with trivalent OPV, and 132 will have been vaccinated with IPV. This trial will evaluate the safety of the candidate vaccines and will assess how the immune system of the volunteers responds to the candidate vaccines. The investigators will take blood specimens and ask the volunteers to provide stool specimens to see how their body responded to the vaccines. In addition, the volunteers will be examined by the investigators to document how well the vaccines were tolerated. The shedding of the candidate vaccines in the vaccinated subjects will also be assessed.

These two nOPV2 candidate vaccines have already been studied in a previous Phase 1 trial at the Univerisity of Antwerp that was performed under contained conditions. The data from this trial confirmed a clear immune response to both candidate vaccines, absence of Serious Adverse Events, and fecal shedding as generally expected for individuals with an IPV-only vaccination history. (See the Section entitled “Knowledge and Experience”). Given this, the proposed trial will be conducted on an out-patient basis. All volunteers will come to the vaccination centre to be seen at least 5 times over 6 weeks.

RESEARCH/DEVELOPMENT ACTIVITIES

PREVIOUS DEVELOPMENT ACTIVITIES

A series of experiments have been performed by several laboratories using mice and monkeys that have suggested that the vaccine candidates are at least as safe as Sabin OPV Type 2. In addition, a Phase 1 clinical trial with healthy subjects who had received IPV in the past has been completed. More information on this trial is provided in the section that follows.

KNOWLEDGE AND EXPERIENCE OBTAINED IN PREVIOUS DEVELOPMENT ACTIVITIES

The first trial using these two candidate vaccines was performed at the University of Antwerp in 2017. Two groups of 15 healthy volunteers agreed to participate in the study. Each group stayed at the quarantine facility where the clinical trial was conducted for approximately 28-35 days after receiving the study vaccines, with telephone follow up at day 42; additional intermittent, follow-up visits to the vaccination centre during the next several weeks were set up for those volunteers who still tested positive for candidate vaccines in their stools. All 15 participants from one group received one candidate vaccine and the other group of 15 received the other candidate vaccine (vaccine candidates #1 or #2).

The safety of each vaccine candidate was evaluated by monitoring each of the volunteers while they were at the facility and for several weeks after leaving the facility. Safety evaluations included assessment for clinical illness and monitoring of blood tests for abnormalities. An independent group of experts monitored information about study safety. In addition to the blood tests for safety, some blood was taken before and 4 weeks after vaccination to study how the volunteers' immune systems responded to the vaccine. In addition, each volunteer was asked to provide daily samples of stool to be tested to see if the vaccine candidate virus was present. This test was done until there was no longer evidence the volunteer was shedding the vaccine virus in 3 consecutive stool samples.

All volunteers completed the study. In general, the two vaccine candidates were well tolerated. There were no serious adverse events reported, and no severe illnesses thought to be due to the candidate vaccines. Most health events reported during the study were generally mild, and all resolved.

Blood tests to assess whether the candidate vaccines resulted in the desired protective response to poliovirus indicated that responses that are likely protective are induced. Most volunteers demonstrated clear immune response to both candidate vaccines.

The stool samples of most of the volunteers tested positive for the candidate vaccines. These observations were anticipated based on experience with Sabin OPV2 from which these candidates were derived. Presence of vaccine virus was observed somewhat more for vaccine candidate #1 than #2. Most volunteers did not have evidence of vaccine virus for more than a month. Some volunteers had more prolonged shedding of vaccine virus in stool, with the longest period for vaccine candidate #1 being almost 3 months and for vaccine candidate #2 just over a month-and-a-half. None of the volunteers demonstrated any illness associated with longer duration of shedding of vaccine virus. Candidate vaccine viruses isolated from a subset of the volunteers' stool samples were tested in mice susceptible to paralysis from polio, in order to see if they had changed after reproducing in the gut. No meaningful changes in ability to paralyze mice were detected in any of these samples. The method used to test for susceptibility to paralysis was designed to readily detect the changes which occur after administration of Sabin OPV2; therefore, these results provide further reassurance that the candidates are likely to be even safer that the licensed Sabin OPV2 vaccines.

FUTURE ACTIVITIES

If the proposed trial confirms that the candidate vaccines are well tolerated by the volunteers, and have a similar effect on the immune system as Sabin OPV2, then the next trial will be started. The data from this proposed trial will provide confidence that the candidate(s) are safe enough to test in younger children (aged 1 to 5 years) and then infants. The trial to be done after the proposed one will be conducted outside of Belgium.

The ultimate goal is for one of these candidate vaccines to replace the current Sabin OPV2 for use in outbreaks of polio type 2 around the world.

BENEFITS

The greatest benefit of these candidate vaccines would be the improved safety over the current Sabin OPV2 vaccine. Each time there is an outbreak of polio and Sabin OPV2 is used, there is

the possibility that there could be a circulating strain of OPV2 that came from the vaccine, that could start another outbreak. The candidate vaccines being studied could offer a significant improvement over Sabin OPV2 if they are more genetically stable than Sabin OPV2, but are as effective in stopping transmission of polio.

RISKS

The candidate vaccines have changes in their genome that are intended to make them more stable. They are designed to be less likely to change after administration to humans and therefore, less likely to cause VAPP, a rare complication of Sabin OPV2. The clinical trials are essential to confirm the protective benefit, safety, as well as the improved stability of the candidate vaccines.

Three main areas of concern have been identified in the risk assessment:

1) The nOPV2 candidate vaccines are dispersed in the environment
   While precautions are taken at the clinical trial centres where the candidate vaccines are administered, shedding via stool may result in the dispersal of the candidate vaccines. The participants who receive the candidate vaccines are likely to shed the vaccine virus in their stool. Survival of shed poliovirus particles in the environment is finite and it is very unlikely that any shed poliovirus particles would remain infectious through dilution and sewage treatment and water purification in Europe.
2) People not involved in the clinical trial are exposed to the nOPV2 candidate vaccine
   Most people in Europe have been vaccinated against polio so they would be protected from infection by any shed virus. Also, all volunteers who enter the study will have been vaccinated as will all their close contacts to ensure no possible risk of disease caused by shed virus.
   There is a very low risk that the virus that is shed in the stools of the volunteers could infect someone who has never been vaccinated against polio or has a suppressed immune system. This is not expected to result in a negative effect for the exposed person, but that person may become a source for further spreading.
3) Participants and/or people not involved in the clinical trial are exposed to a virulent form derived from a nOPV2 candidate vaccine
   One of the issues with the existing Sabin 2 vaccine is the reversion to a stronger form. The likelihood that this occurs is deemed low: the candidate vaccines have been engineered with a combination of changes which make reversion to a dangerous form unlikely. This statement is supported by observations from the Phase 1 study that no meaningful increases in potential to paralyze susceptible mice were detected in vaccine virus isolated from volunteers' stool samples. Finally, the overall vaccination status is very high in Belgium and the EU, which means that even in the case of an exposure, the health impact would be negligible.

CONTAINMENT, CONTROL AND MONITORING MEASURES

Measures will be taken to avoid exposure of the study site staff from the candidate vaccines as well as dispersal of any unused candidate vaccines. These include precautions during the dispensing and administration of the candidate vaccines to the volunteers, disposal of contaminated materials, and site cleaning. The clinical staff received a recent IPV booster. When

handling or administering the vaccines, they will wear lab coats and disposable gloves. Disposable wipes will be used when handling samples. All waste material will be handled as hazardous medical waste. In addition cleaning agents that will destroy any poliovirus will be used.

The selection of volunteers will be made carefully. Only healthy participants who have been vaccinated with either IPV or OPV will be allowed to enter the study. There are other criteria that would exclude a volunteer from participating in the study in order to limit the risk of further exposure. These include volunteers who have household or professional contact with someone with a suppressed immune system or someone who is not fully immunized against polio. The volunteers will be carefully monitored during the study and any adverse events will be managed by the clinical staff at the site.

In addition, the volunteers will be instructed to use good hygiene practices that include flushing the toilet with the lid closed, and hand washing after having been to toilet and before preparing food. Stools will be disposed of via the sewage system, in which it will be immediately diluted. Sewage treatment as commonly practiced is expected to substantially reduce virus concentrations.

CONTROL OF GMM AND GENE SPREADING

The viability of the shed vaccine virus is unknown, but it is likely to be similar to that of Sabin OPV2. Survival outside of a human host is finite and depends on physical, chemical and biological factors in the environment. It has been estimated by the WHO that at ambient temperatures a 90% decrease in infectivity is expected every 5.5 days in fresh water and every 2.5 days in seawater (Dowdle and Birmingham, 1997). And, as noted above, sewage treatment as commonly practiced is expected to substantially reduce virus concentrations.

The risk of human to human spread of the candidate vaccine viruses is very low. Specific hygienic practices of the volunteers will limit that spread, as will the careful handling and disposal of any vaccine vials or contaminated material.

Because humans are the primary host of polioviruses, there is little risk of transfer of the genes to other microorganisms. However, if a volunteer was infected with a virus from the same family as polio (known as type C enteroviruses) at the same time that they received the vaccine candidate, it would be possible for an exchange of genetic material between the two viruses to occur. This is a negligible risk because only healthy volunteers will be enrolled and there is no evidence of circulation of type C enteroviruses in the Belgian population in recent years. Infection with the two viruses at the same time would be a very rare event, and therefore the risk is extremely low/negligible.

Polioviruses replicate only in the cytoplasm of an infected cell and therefore there is no risk of incorporation of the GMM into the host DNA. Unlike most genetically modified microorganisms, the two nOPV2 candidate vaccines do not contain genes from other organisms. As a result there is no risk of spread of those genes.

GENETIC STABILITY OF THE GMM

There have been several modifications made to the two candidate vaccines to help improve the genetic stability as compared to Sabin OPV2. Scientists have identified the section of the genome in Sabin OPV2 that is most likely to change to result in clinical disease. In the candidate vaccines, that section of the genome has changes that would require multiple different mutations to make it a virus that could cause polio. Laboratory experiments show that the two nOPV2 candidate vaccines are more stable than Sabin OPV2. Stability against changes to a dangerous form also was confirmed in a subset of stool samples from the Phase 1 clinical study.

DESTRUCTION OF GMM CONTAINING MATERIAL

This notification concerns a deliberate release of two novel oral polio candidate vaccines. This release is for experimental purposes and use of this material for any other purpose is prohibited. The vaccines will be administered in study site areas with controlled and restricted access. The remaining vaccines will be destroyed at the end of the study.

TRAINING REQUIREMENTS

The staff at the sites are trained in Good Clinical Practices which includes how to handle the investigational products and how to administer oral vaccines. All staff members have many years of experience in conducting vaccine trials and follow regularly GCP training. Volunteers are systematically instructed about the hygienic measures to respect and the inclusion/exclusion criteria are carefully reviewed at each visit.

EMERGENCY SITUATIONS

Any material that has been exposed to the candidate vaccines will be disinfected using a chemical that will kill polioviruses, or will be inactivated as hazardous medical waste. At the clinical trial sites, any spill of the vaccine will be cleaned up with appropriate chemical disinfection. All materials used in the clean up process will be disposed of in a controlled manner. Even in case of a spill, the risk of exposure to the general public is very small.

OTHER CONTAINMENT, CONTROL AND MONITORING MEASURES

RESPONSIBILITIES OF THE NOTIFIER

The consent that could be given to the notifier by the competent Minister stipulates that the notifier takes complete civilian liability regarding the damage that could be caused by the deliberate release to the health of humans, animals or environment.

INSPECTION BY THE PUBLIC AUTHORITIES

Inspectors are in charge of inspecting the trials for compliance with the conditions specified in the consent and to investigate potential breaches of the consent. If mismanagement or fraud is identified, specific sanctions will be imposed.

ACTIVITY REPORT

At the end of the trial an activity report prepared by the notifier needs to be delivered to the competent authority. This activity report includes at least the following data:

- The site and period of release,
- The precise nature of the actually released GMMs,
- The aim(s) of the trial,
- The measures that were taken to prevent unwanted release of transgenic material,
- If applicable, the measure that were taken to protect the subject during administration of the GMM-containing study drug,
- If applicable, the measures that were taken to protect the relatives of the treated subjects,
- The measures that were taken to protect the workers who had to manipulate the GMM-containing material,
- The results obtained during the trial,
- An overview of the monitoring of the subjects for GMM shedding,
- An overview of the monitoring of GMM or recombinant DNA in the environment.

REFERENCES

- Alexander LN, Seward JF, Santibanez TA, Pallansch MA, Kew OM, Prevots DR, Strebel PM, Cono J, Wharton M, Orenstein WA and Sutter RW (2004) Vaccine policy changes and epidemiology of poliomyelitis in the United States. JAMA 292(14):1696-701.
- Dowdle WR and Birmingham ME (1997) The biologic principles of poliovirus eradication. J Infect Dis. 175 Suppl 1:S286-92.

GLOSSARY

Adverse event	Any unfavorable or unintended symptom or disease associated with the use of a drug or vaccine, whether or not it is considered related to the drug or vaccine
Attenuated	Weakened
Cytoplasm	The material within a living cell, excluding the nucleus
Deoxyribonucleic acid (DNA)	The carrier of genetic information present in cells
Candidate vaccines	Vaccines that have not been licensed by a national regulatory authority
Feco-oral transmission	Ingestion (through the mouth) of food and water contaminated with an infectious agent that was derived from the stool of an infected person
Genome	The complete set of genes or genetic material in a cell or organism
Inactivated	Killed or no longer active
Inactivated Polio Vaccine (IPV)	A vaccine that prevents infection with poliovirus. The vaccine is made from an inactivated polio virus and is administered by intramuscular (in the muscle) injection.
Infectious	Is able to cause an infection

Phase 1 study or trial	The testing of a drug or vaccine in a small group of healthy volunteers to assess safety
Poliomyelitis (also referred to as polio)	A highly contagious viral disease caused by one of the three types of the polio virus
Sabin bivalent OPV (Sabin bOPV)	Sabin OPV that includes polioviruses Types 1 and 3 in a weakened (or attenuated) form
Sabin Oral Polio Vaccine (Sabin OPV)	A vaccine that prevents infection with poliovirus. The vaccine is made from a weakened (or attenuated) virus that is unlikely to cause clinical disease, and is administered as drops in the mouth.
Sabin trivalent OPV (Sabin tOPV)	Sabin OPV that includes all three types of polioviruses in a weakened (or attenuated) form
Serious Adverse Event (SAE)	An adverse event that is life threatening or results in: death, hospitalization (or prolongs hospitalization), a congenital anomaly, persistent or significant disability or incapacity, or required intervention to prevent permanent impairment
Stool specimen	A small sample of a bowel movement
The Immune System	A network of cells and tissues that work to protect against infections
Type C enteroviruses	A group of viruses that include poliovirus, coxsackie virus and others
Vaccine-associated paralytic polio (VAPP)	Paralytic polio case in a OPV vaccinated person, or person who is in contact with the vaccinated person. This disease is associated with a mutation in the poliovirus vaccine strain.
Wild type	The natural form of a virus

CONTACT

If you have any comment on the public dossier or our activities, or wish to obtain additional information on the deliberate release, please contact us at the following address:

You can also have access to a summary of the notification (SNIF) on the website of the Joint Research Centre of the European Commission (http://gmoinfo.jrc.ec.europa.eu/). Comments can be addressed to the Commission via this website.

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