MedImmune

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INFORMATION FOR THE PUBLIC

MI-CP178: Study of a Live, Attenuated Intranasal Vaccine Against Respiratory Syncytial Virus (RSV) and Parainfluenza Virus Type 3 (PIV3), in Healthy 6 to < 24 Month-Old Children and in 2 Month-Old Infants.

European Notification Number
B/BE/08/BVW1

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1. REGULATORY FRAMEWORK AND AUTHORIZATION PROCEDURE

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 the Royal Decree of 21 February 2005 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.

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 company MedImmune, LLC submitted an application dossier to the competent authority. On the basis of the advice of the Biosafety Council, the competent minister could grant permission to the company MedImmune, LLC to conduct experiments with recombinant vaccine MEDI-534 as stipulated in the application B/BE/08/BVW1.

The release will take place at locations in Flanders and Brussels as a consequence of clinical trials conducted at UZ Brussel, Laarbeeklaan 101, 1090 Brussels and St-Vincentiusziekenhuis, Sint-Vincentiusstraat 20, 2018 Antwerp. It is expected to start in April 2009 and to be completed by March 2012.

2. DESCRIPTION OF THE GENETICALLY MODIFIED MICRO-ORGANISM (GMM)

Respiratory syncytial virus (RSV) and human parainfluenza virus type 3 (hPIV3) are important causes of severe lower respiratory tract illness. The GMO, MEDI-534 (b/h PIV3/RSV F2), is a recombinant vaccine which expresses human PIV3 fusion (F) and hemagglutinin-neuraminidase (HN) proteins in a bovine PIV3 (bPIV3) virus genomic backbone. In addition, the human RSV fusion protein (RSV F) has been engineered into the genome. Thus, the bPIV3 backbone is used to deliver antigens thought to be protective against both RSV and hPIV3 infection. MEDI-534 is a live attenuated vaccine. It contains living PIV3 virus that is weakened and a part of the RSV virus that by itself does not cause RSV illness.

The viral backbone of MEDI-534, bovine PIV3, is related to hPIV3 but is not virulent in humans. The bPIV3 strain that serves as a backbone for the MEDI-534 vaccine naturally occurs in cows. Bovine PIV3 is endemic throughout Europe and is among the most frequently diagnosed virus in bovine respiratory disease cases.

MEDI-534 vaccine will be administered to children 6 to <24 months of age and infants 2 months of age. MEDI-534, as with bPIV3, hPIV3, RSV and other respiratory viruses, is transmitted through the mucous membranes of the eyes, mouth, or nose. MEDI-534 initiates a lytic sub-clinical infection in the nasal passages that is rapidly cleared by the immune response. MEDI-534 does not result in a persistent infection, and the window of viral replication is anticipated to be limited. Study subjects will be administered either MEDI-534 vaccine or placebo intranasally. The mechanism of action of MEDI-534 is to mimic the immunologic responses stimulated by natural infection by replication in the nasal passages of the host upon administration. Therefore, viral replication of MEDI-534 in vaccine recipients is necessary for generation of an immune response.

3. TYPE AND PURPOSE OF THE ENVISAGED TRIAL

The objectives of this study are to describe the safety, immune response and viral shedding of multiple doses of MEDI-534 in RSV and PIV3 seronegative children 6 to < 24 months of age and in infants 2 months of age. The study will be conducted in North America, South America, Europe, Africa, and Australia/New Zealand and is currently ongoing in the United States. The study will enroll 720 subjects globally and it is anticipated that 7 countries within the EU will be involved.

The study will be conducted at standard healthcare facilities where paediatric vaccines are commonly administered. Within Belgium, the study will take place at two clinical sites; UZ Brussel, Laarbeeklaan 101, 1090 Brussels, and St-Vincentiusziekenhuis, Sint-Vincentiusstraat 20, 2018 Antwerp. It is anticipated that a total of 20-30 subjects will be enrolled at the sites.

The intention of this study is to add to scientific/clinical knowledge by continuing to expand the safety profile of MEDI-534 in both young seronegative children 6-24 months of age and infants 2 months of age. Additionally, evaluation of the immune response generated by administration of multiple doses of MEDI-534 will provide an initial indication of the biological activity of MEDI-534. The dosage that will be used for further development will be selected based on data from this trial.

Each subject in the study will receive three doses of either MEDI-534 or matched placebo, at intervals of approximately two months. Given the dose schedule it is not possible for the subjects to remain within contained facilities for the duration of the study.

4. RESEARCH/DEVELOPMENT ACTIVITIES

In animal model systems, MEDI-534 has been shown to be safe and well-tolerated. MEDI-534 has been previously evaluated in two completed Phase 1 clinical trials in the United States. Overall, the data from clinical testing in healthy adults and RSV and PIV3 seropositive children 1 to 9 years of age suggest that MEDI-534 has an acceptable safety profile and restricted replication in seropositive subjects. MEDI-534 is also currently being evaluated in an on-going Phase 1 study that evaluates the safety, tolerability, immunogenicity and shedding of MEDI-534 in seronegative children 6 to <24 months of age. A preliminary blinded evaluation after 2 doses of MEDI-534 indicates that the vaccine was well tolerated in hRSV and hPIV3 seronegative infants 6 to <24 months of age. This study is currently enrolling subjects within the United States.

Clinical study MI-CP178, the same study proposed under this application, has also been initiated in the United States. Study MI-CP178 will expand the safety database in the RSV/PIV3 seronegative population before advancing to a proof of concept vaccine study.

5. POTENTIAL BENEFITS OF THE PLANNED RELEASE

RSV is the single most important cause of severe lower respiratory tract illness (LRI) in infants and young children and is estimated to cause as much as 90% of all childhood bronchiolitis and up to 40% of all pediatric pneumonias, both associated with substantial morbidity and mortality (Hall 2000). The most severe RSV illness occurs in the youngest infants (Hall 2000). In addition to being the leading cause of serious LRI in young infants, RSV has also been associated with long-term complications such as wheezing and asthma up to early adolescence (Sigurs 2005). RSV is endemic throughout the world and all individuals are serially exposed to RSV.

Human parainfluenza virus type 3 (hPIV3) is another important cause of lower respiratory tract disease. PIV3 is endemic throughout the world and all individuals are serially exposed to PIV3.

Currently no vaccine exists for the prevention of RSV or hPIV3 respiratory tract infection and disease. Because RSV and hPIV3 infects and can cause disease in otherwise healthy infants, the development of vaccines for the prevention of RSV disease is a public health priority (WHO 2007). Thus, MEDI-534 has the potential to fulfill a currently unmet medical need.

6. ASSESSMENT FOR POTENTIAL RISKS FOR HUMAN HEALTH AND THE ENVIRONMENT

Potential Risks to Human Health

MEDI-534 vaccine is a live, attenuated virus that requires a specific host cell for replication. The virus does not persist in the environment and can only remain infectious outside of a host cell for no more than 8 hours. Other factors such as sunlight and heat will further decrease its chance of survival outside a host cell. It is susceptible to common disinfectants and cleaning agents. MEDI-534 is considered to have minimal potential hazard to clinical site personnel and the environment. No laboratory manipulation of MEDI-534 vaccine or placebo will be conducted at the clinical study sites. Procedures are in place for the shipping, storage, administration and disposal of MEDI-534, and appropriate site training is conducted on study procedures.

Replication of MEDI-534 in the nasal mucosa is required to generate an immune response. Thus, it is expected that RSV and PIV3 naïve recipients will shed vaccine virus through nasal secretions. Although viral shedding is very restricted in seropositive individuals, the magnitude and duration of viral shedding for MEDI-534 in RSV and PIV3 seronegative children is still unknown. Shedding of MEDI-534 leading to secondary transmission is possible with potential secondary transmission to vulnerable populations such as pregnant women, immunocompromised individuals and seronegative children. The study exclusion criteria outlined in the protocol exclude subjects from participation if they have the potential to come into contact with individuals considered to be at risk for secondary transmission of MEDI-534 should a subject shed vaccine virus. These exclusion criteria provide a guideline for the extent of contact that should be avoided to minimize the risk of transmission to these populations. RSV and PIV3 are endemic throughout the world and all people can expect to be serially exposed on an annual basis.

MEDI-534 initiates a lytic sub-clinical infection in the nasal passages that is rapidly cleared by the immune response. MEDI-534 does not result in a latent or persistent infection. Paramyxoviruses, such as RSV and hPIV3 replicate in the cell cytoplasm and do not integrate into the host genome (Bukreyev 2006). Furthermore, the absence of any human gene sequences and the absence of any MEDI-534 encoded retroviral polymerase means that the genome of MEDI-534 remains as RNA throughout its lifecycle. Without the ability to convert RNA to DNA and the absence of human gene sequences, integration of any MEDI-534 genetic material into the host genome is highly improbable.

During the conduct of the study, subject safety will be monitored by the collection of solicited symptoms, adverse events, serious adverse events, concomitant medication use, medically attended lower respiratory illness, and significant new medical conditions. Additionally, viral shedding will be monitored by the collection of nasal wash specimens at defined intervals and during illness visits, and immunogenicity will be evaluated through the collection of serum samples at defined intervals.

Potential Risks to the Environment

The potential for MEDI-534 interaction with other organisms in the environment would be limited to viral shedding and secondary transmission via shared nasal secretions with vaccinated infants. MEDI-534 cannot infect microbes or plant cells which lack receptors for hPIV3 F and HN proteins, which are the proteins responsible for attachment and entry of MEDI-534 into host cells. The bPIV3 Kansas/15626/84 strain that serves as a backbone for the MEDI-534 recombinant vaccine naturally occurs in cows and causes respiratory diseases in calves; however, bPIV3 is endemic throughout Europe. Virulence of MEDI-534 in bovines has not been studied; however, transmission to animals would require the sharing of nasal secretions from vaccinated infants with the animal.

Recombination events are extremely rare for paramyxoviruses and have not been reported in nature. There is minimal risk of gene exchange between circulating wild-type and vaccine virus (Bukreyev 2006).

The study will be conducted at standard healthcare facilities where paediatric vaccines are commonly administered. It is not anticipated that the study vaccine or any waste associated with study procedures will affect the surrounding ecosystem.

Destruction of GMM Containing Material

All unused study vaccine will be returned to MedImmune's central storage depot in the UK or disposed of at the clinical site upon authorization of MedImmune. All vaccine and placebo syringes, nasal wash collection kits and components, needles, and other biomedical waste generated during the conduct of the study will be discarded into appropriate biohazard waste containers and disposed of at the study site according to site procedures. MEDI-534 is susceptible to common disinfectants, 1% sodium hypochlorite, 70% ethanol, 2% glutaraldehyde and detergents, and physical inactivation is rapidly achieved by UV irradiation and steam sterilization.

Training Requirements

All principal investigators and sub-investigators participating in the study will be qualified by education, training and experience to assume responsibility for the proper conduct of the trial. Clinical sites where the study is to be conducted will be thoroughly evaluated prior to the initiation of the study to ensure that the facilities are sufficient for storing and administering the vaccine, as well as having the appropriate facilities for the

collection and storage of human specimens (nasal wash and serum samples). Additionally, all clinical site personnel involved in the handling or administration of study vaccine will be trained accordingly.

Emergency Situations

Procedures are in place to avoid and/or minimize the spread of MEDI-534 by controlled containment of MEDI-534 during transport and at the clinical sites, monitoring of viral shedding from study subjects throughout the duration of the trial, and minimizing the potential of secondary transmission to vulnerable populations through exclusion criteria defined in the study protocol. If decontamination procedures are deemed necessary for any reason, such as in the event of a spill, a freshly prepared 1:10 solution of household bleach (~3.5% sodium hypochlorite) and water can be used.

This notification concerns a deliberate release of GMM for experimental purposes. Therefore, the use of this material for any other purpose is prohibited.

7. 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.

8. 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. In case where mismanagement or fraud is identified specific sanctions will be imposed.

9. ACTIVITY REPORT

At the end of the trial an activity report prepared by the notifier needs to be delivered to the competent authority. The 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 measures 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 patients
- the measures that were taken to protect the workers who had to manipulate the GMM-containing material
- the method used for the destruction of the unused or contaminated material

- the results obtained during the trial, an overview of the monitoring of patient for GMM shedding
- an overview of the monitoring of GMM or recombinant DNA in the environment.

10. REFERENCES

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Hall CB, McCarthy CA. Respiratory syncytial virus. In: Mandell GL, Bennett JE, Dolin R (eds). Principles and practice of infectious diseases (5th edition). New York, Churchill Livingstone, 2000; pp. 1782-1801.

Sigurs N, Gustafsoon PM, Bjarnason R, Lundberg F, Schmidt S, Sigurbergsson F and Kjellman B. Severe Respiratory Syncytial Virus Bronchiolitis in Infancy and Asthma and Allergy at Age 13. Am. J. Respir. Crit. Care Med. 2005;171:137-141.

World Health Organization. The Initiative for Vaccine Research. Strategic Plan 2006-2009. Available at: http://www.who.int/vaccine_research/en/. Accessed 18 December 2007.

11. GLOSSARY

"genetic modification" in relation to an organism means the altering of the genetic material in that organism in a way that does not occur naturally by mating or natural recombination or both

“lytic” of, relating to, or causing lysis: *a* lytic *enzyme.*

"organism" means a biological entity capable of replication or of transferring genetic material and includes a micro-organism, but does not include a human or a human embryo

12. 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.

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