Saap. 18.6.2013
1/MA/08

PPD

Sosiaali- ja terveysministeriö
Geenitekniikan lautakunta
PL 33
Kirkkokatu 14
00170 Helsinki
Finland

17Jun2013

Re: Report on the Results of Deliberate Release in Finland

Study drug: MEDI-534

Protocol Title: A Phase 1/2a, Randomized, Double-Blind, Placebo-Controlled, Dose-Escalation Study to Evaluate the Safety, Tolerability, Immunogenicity and Vaccine-like Viral Shedding of MEDI-534, 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

Protocol Number: MI-CP178

EudraCT Number: 2008-002651-24
Application Number: 001/MA/2008

Dear Sir/Madam,

On behalf of our client, MedImmune LLC, we wish to provide you the Report on the Results of Deliberate Release in Finland.

MedImmune is not currently intending to submit an application for placing MEDI-534 on the market within the EU at this time. This type of information is not typically known until later in product development following a complete assessment of all clinical, nonclinical and quality data collected across the development cycle. In addition, the knowledge of whether or not a company plans to pursue marketing of an investigational medicinal product is considered to be confidential business information with potentially significant impact to the financial value of the company. For these reasons, the details of any plans to submit a marketing application within the EU have not been incorporated into the publicly releasable document but are being shared for transparency with this agency.

Should you have any questions regarding this submission, please do not hesitate to contact Principal CRA Seija Reivolahti PPD Scandinavia AB, c/o Orvokkikatu 10, 21110 Naantali. Phone: 040 830 9461 E-mail: seija.reivolahti@ppdi.com

Yours faithfully,

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Attachments:

1. Finland GMO Report Finnish and English

Report on the Results of Deliberate Release in Finland (Study MI-CP178)

1 Introduction

In accordance with Section 19 of the Gene Technology Act, MedImmune is submitting results of deliberate release for the clinical trial conducted under protocol MI-CP178 in Finland with the investigational medicinal product, MEDI-534. MEDI-534 is classified as a genetically modified organism and is a live, attenuated intranasal vaccine candidate being studied for the prevention of lower respiratory tract illness caused by respiratory syncytial virus (RSV) and parainfluenza virus type 3 (PIV3) in children. MEDI-534 is a chimeric vaccine expressing human PIV3 fusion and hemagglutinin-neuraminidase proteins in a bovine PIV3 viral backbone. In addition, the human RSV fusion protein has been engineered into the genome.

2 Background Study Details

EudraCT Number:	2008-002651-24
GTB Application Number:	001/MA/2008
European Notification Number:	B/FI/08/1MA
Study Number:	MI-CP178
Study Title:	A Phase 1/2a, Randomized, Double-blind, Placebo Controlled, Dose-escalation Study to Evaluate the Safety, Tolerability, Immunogenicity and Vaccine-like Viral Shedding of MEDI-534, 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
Study Start Date:	Overall global study: 11 July 2008 (date of signed informed consent for first randomized subject) Within Finland: 06 July 2009 (date of signed informed consent for first randomized subject)
Last Subject Visit/Completion Date:	Overall global study: 23 August 2012 Within Finland: 02 February 2012

Methodology:

This was a randomized, double-blind, placebo-controlled, multidose, multicenter, dose-escalation study to evaluate the safety, tolerability, vaccine-like viral shedding, immunogenicity, and genotypic stability of MEDI-534 in healthy subjects 6 to < 24 months of age and 2 months of age. MEDI-534 was initially administered at a dosage level of 10^5 $TCID_{50}$ to RSV and PIV3 seronegative subjects 6 to < 24 months of age (Cohort 1) and, subsequently, at dosage levels of 10^6 $TCID_{50}$ in the same population (Cohort 2) and, in parallel, at 10^4 $TCID_{50}$ in subjects 2 months of age not screened for baseline serostatus (Cohort 3). Clinical testing of MEDI-534 in subjects 2 months of age not screened for baseline serostatus continued in a dose-escalation fashion with dosage levels of 10^5 and 10^6 $TCID_{50}$ (Cohorts 4 and 5, respectively). Each cohort was to be randomized in a 1:1 ratio of MEDI-534 to placebo. All subjects were to be followed for a total of 365 days (1 year) from receipt of the first dose of investigational medicinal product (IMP) to allow for all subjects to be followed for safety when RSV circulates irrespective of local epidemiology.

Study Objectives:

The primary objective of this study was to describe the safety and tolerability of multiple doses of MEDI-534 in RSV and human PIV3 in seronegative children 6 to < 24 months of age and in unscreened infants 2 months of age. Secondary objectives included the following:

- To describe the incidence and magnitude of MEDI-534 vaccine-like virus shedding after each dose.
- To evaluate the immune response generated by multiple doses of MEDI-534.
- To evaluate the genotypic stability of recovered vaccine virus.
- To describe the incidence of serious RSV disease in vaccinated subjects through the end of the study reporting period.

Demographics:

MEDI-534 was studied in a total of 80 study centers and a total of 720 subjects were enrolled in Australia, Brazil, Canada, Finland, Germany, Israel, Spain, South Africa, and the United States of America from 11 July 2008 until study completion on 23 August 2012. A total of 17 subjects were enrolled at 5 sites in Finland (see Table 2-1 below). The national coordinating investigator was located in Tampere.

Table 2-1 Finnish Clinical Sites Participating in Study MI-CP178

Site ID	Locality	Number of Subjects Enrolled	
		6 - <24 months	1-3 months
4356	Lahti	1 Placebo	2 MEDI-534 3 Placebo
6753	Helsinki	1 MEDI-534	2 MEDI-534 2 Placebo
6808	Tampere	1 MEDI-534 1Placebo	0
6822	Pori	1 MEDI-534	1 MEDI-534 1 Placebo
6826	Kuopio	0	1 MEDI-534
4364	Kokkola	0	0
6708	Turku	0	0
6767	Järvenpää	0	0
6835	Oulu	0	0

3 Regulatory Approvals in Finland

The Finnish National Agency for Medicines granted approval to conduct Protocol MI-CP178 on 19 December 2008.

On 12 February 2009, the Finnish Board of Gene Technology granted permission for the deliberate release of MEDI-534 into the environment for the period of time between 1 April 2009 and 31 December 2012.

4 Summary of Investigational Medicinal Product Imported

The following table summarizes the number of kits of IMP (MEDI-534 and placebo) that were shipped to Finland per site over the course of the study.

Table 4-1 Number of Kits Shipped to Finnish Clinical Sites

Site ID	Site Name	Number of Kits Received
4356	Tampere University/Lahti Vaccine Research Clinic	26
4364	Tampere University/Kokkola Vaccine Research Clinic	8
6708	Tampere University/Turku Vaccine Research Clinic	18
6753	Tampere University/South Helsinki Vaccine Research Clinic	32
6767	Tampere University/ Järvenpää Vaccine Research Clinic	14
6808	Tampere University/ Tampere Vaccine Research Clinic	20
6822	Tampere University/Pori Vaccine Research Clinic	14
6826	Tampere University/Kuopio Vaccine Research Clinic	14
6835	Tampere University/Oulu Vaccine Research Clinic	4

Per the protocol, all unused study IMP was either returned to MedImmune's storage depot in the United Kingdom (Aptuit, Bathgate, Scotland) or was destroyed according to institutional biohazard procedures at the respective clinical site upon authorization by MedImmune. All shipments of expired/unused IMP from the sites to the depot have been reconciled, and it is confirmed that no IMP remains in Finland as of 22 March 2013.

5 Risk Management Measures Used During the Release

Transport of study vaccine was conducted in accordance with GMO transport guidelines and IATA regulations. Study vaccine was transported in sealed primary containers packed within secondary sealed and unbreakable containers marked with a label to indicate that they contained GMOs. Study vaccine was stored at -60°C or below in the original outer package and stored in a secure location with limited access. Instructions and emergency response plans were established for clean-up and decontamination in the event of an accidental spill or leakage of study vaccine.

Study vaccine was administered by qualified, medically trained professionals at licensed healthcare facilities with standard facility controls in place for administration of pediatric vaccines, collection of samples and clinical evaluation of study subjects. Site personnel

involved in the handling or administration of study vaccine were appropriately trained. No laboratory manipulation of MEDI-534 vaccine or placebo was conducted at these study sites. MEDI-534 did not require any special safety containment above universal precautions due to its biosafety classification. Used study vaccine syringes, nasal wash collection kits and components, needles, and other biomedical waste generated during the study was placed immediately into locked containers or sealed bags and retained for accountability. Upon reconciliation and accountability, study waste was destroyed by returning the material to the central storage depot, by following institutional procedures for the disposal of biohazardous material, or by sterilizing by steam for 30 minutes at 121°C.

Because MEDI-534 is a live attenuated vaccine, replication of the vaccine virus in the nasal passages is expected in order to generate an immune response, and thus, it was anticipated that RSV and PIV3 naïve recipients would shed vaccine virus through nasal secretions (deliberate release). Study subjects were monitored for viral shedding by the collection of nasal wash specimens at defined intervals during the study, and during any unscheduled illness visits. The study exclusion criteria excluded subjects from participation if they had the potential to come into meaningful 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. Immunogenicity was also evaluated through the collection of serum samples at defined intervals, and safety monitoring of the study subjects was conducted through the duration of the study. Solicited symptoms, adverse events, serious adverse events, concomitant medication use, medically attended lower respiratory illness, and significant new medical conditions data were collected.

There were no possible exceptions from the original release plan (also refer to Section 6 below).

6 Unintended Release of the Genetically Modified Organism (MEDI-534)

Due to study blinding any spill or breach of container of IMP was to be treated as an unintended release of the GMO, and appropriate containment measures were to be followed. Clinical sites were instructed to notify the sponsor and its local designee if any spillage or breach of container occurred. There were no GMO unintended releases reported with the study IMP in Finland.

7 Results of Deliberate Release

Study MI-CP178 is completed and a final clinical study report is currently in preparation. However, a summary of the results of the deliberate release that are associated with potential risks to human or animal health or environment are being provided below.

A total of 720 subjects in 9 countries participated in the global study from 11 July 2008 to 23 August 2012 (of these subjects, 17 were from sites in Finland). Approximately 90% of the 320 subjects in the 6 to < 24 months of age cohorts completed the study and approximately 94% of the 400 subjects in the 1-3 month old cohorts completed the study; nearly all subjects who were dosed were followed through 28 days post each dose. No subject discontinued the study for safety reasons.
For note, of the 720 subjects enrolled into the global study, 17 were from sites in Finland; of the 17 subjects in Finland, 8 (47.0%) received placebo and 9 (52.9%) received MEDI-534 (Table 2-1).

Vaccine-type virus shedding was expected and detected in nasal wash samples over a short period after dosing and occurred predominately after Dose 1; very few subjects shed post Dose 2 or post Dose 3. No placebo subjects shed vaccine type virus. The incidence of solicited symptoms and treatment-emergent adverse events, collected per the study protocol, do not suggest any major safety concerns and the events observed were primarily expected to occur in the enrolled subject population. There was no evidence of classical enhanced RSV disease.

8 Assessment of Risk Following Completion of Deliberate Release

Prior to the study, MEDI-534 was considered to have minimal potential hazard to clinical site personnel and the environment. As described in the original risk assessment, MEDI-534 vaccine is a live, attenuated virus that requires a specific host cell for replication. The intended receiving environment for MEDI-534 was the upper respiratory tract of a trial subject who had received the product in an appropriately controlled setting. The virus does not persist in the natural environment and can only remain infectious outside of a host cell for 8 hours or less. Factors such as sunlight and heat will further decrease its chance of survival outside of a host cell and it is susceptible to common disinfectants and cleaning agents. No evidence exists of MEDI-534 being transmitted from humans to animals or vice versa, and MEDI-534 is not expected to infect microbes or plant cells.

Following completion of this study (deliberate release), there were no observed effects/interactions of the GMO which were linked to unanticipated risks on human and animal health and environment. Anticipated effects of deliberate release included shedding of MEDI-534 from trial subjects after vaccine administration, and the clinical data support the

previous assessment that the window of viral replication would be limited with low risk of secondary transmission.

9 Conclusions

Based on the available data to date for Study MI-CP178, the risk evaluation for this trial has not changed since the time of initial approval within Finland. The data collected for this study continues to support MedImmune's statement that there is no reason to assume that this study posed a risk to human or animal safety or the environment. Vaccine-type virus shedding was expected and detected in nasal wash samples over a short period after dosing and occurred predominately after Dose 1; very few subjects shed post Dose 2 or post Dose 3. No placebo subjects shed vaccine type virus. In addition, the incidence of SSs and TEAEs do not suggest any significant safety concerns and the events observed were primarily expected to occur in the enrolled subject population. The likelihood the vaccine virus was transmitted to study subject contacts or the environment remains very small because of MEDI-534's known attenuation profile (due to host range restriction of the bovine PIV3 backbone), lack of shedding in placebo subjects and no reports of unintended release.

No marketing notification is intended under Directive 2001/18/EC at this time, as the deliberate release was for investigational purposes only.