PART 1 (COUNCIL DECISION 2002/813/EC)

SUMMARY NOTIFICATION INFORMATION FORMAT FOR THE RELEASE OF GENETICALLY MODIFIED ORGANISMS OTHER THAN HIGHER PLANTS IN ACCORDANCE WITH ARTICLE 11 OF DIRECTIVE 2001/18/EC

In order to tick one or several possibilities, please use crosses (meaning x or X) into the space provided as (.)

A. General information

1. Details of notification

(a)	Member State of notification	UK
(b)	Notification number	B/GB./09./R43/01
(c)	Date of acknowledgement of notification	12/06/2009
(d)	Title of the project	Clinical Study MI-CP178, "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"….
(e)	Proposed period of release	From 01/04/2009 until 31/03/2012

2. Notifier MedImmune LLC
Name of institution or company: …

3. GMO characterisation

(a) Indicate whether the GMO is a:

viroid		(.)
RNA virus		X
DNA virus		(.)
bacterium		(.)
fungus		(.)
animal		
-	mammals	(.)
-	insect	(.)
-	fish	(.)
-	other animal	(.)

specify phylum, class …

(b) Identity of the GMO (genus and species)
Bovine Parainfluenza virus type 3 (bPIV3) plasmid 'backbone': Respirovirus genus
Human Parainfluenza virus type 3 (hPIV3) F and HN genes: Respirovirus genus
Respiratory Syncytial virus (RSV) F gene: Pneumovirus genus

(c) Genetic stability – according to Annex IIIa, II, A(10)
Studies in cell culture and hamsters indicate that the nonessential RSV F gene is maintained without genetic alterations through multiple passage in vitro and in vivo.

4. Is the same GMO release planned elsewhere in the Community (in conformity with Article 6(1)), by the same notifier?
Yes X No (.)
If yes, insert the country code(s) BE, ES, FR, DE, IT, FI

5. Has the same GMO been notified for release elsewhere in the Community by the same notifier?
Yes (.) No X
If yes:
- Member State of notification …
- Notification number B/../../…

Please use the following country codes:
Austria AT; Belgium BE; Germany DE; Denmark DK; Spain ES; Finland FI; France FR; United Kingdom GB; Greece GR; Ireland IE; Iceland IS; Italy IT; Luxembourg LU; Netherlands NL; Norway NO; Portugal PT; Sweden SE

6. Has the same GMO been notified for release or placing on the market outside the Community by the same or other notifier?
Yes (.) No X
If yes:
- Member State of notification …
- Notification number B/../../…

7. Summary of the potential environmental impact of the release of the GMOs.
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 cannot remain infectious outside of a host cell for 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.

MEDI-534 has been shown to be safe and well-tolerated in model animal systems and in clinical studies conducted in the United States in adults and seropositive children. MEDI-534 is a live viral vaccine, and replication of the vaccine virus 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. Study procedures are in place to both monitor viral shedding during the trial, as well as to assure that subjects with the potential to come into contact with individuals considered to be at risk for secondary transmission of shed virus will be excluded from participation. Subject safety will be monitored through the duration of the trial.

The bPIV3 strain that serves as a backbone for the MEDI-534 vaccine naturally occurs in cows and has been shown to cause respiratory disease in calves. 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.

The study will be conducted at standard healthcare facilities where paediatric vaccines are commonly administered. 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, processing and storage of human specimens (nasal wash and serum samples). Additionally, the study protocol provisions for some post-dosing study visits to be conducted in the home of subjects. In-home visits will be conducted by qualified and trained site personnel. The visit will consist of a clinical evaluation of the study subject, as well as the collection of human specimens (nasal wash and serum samples). Specimens obtained in the home will be collected according to the study-specific laboratory manual and promptly transported to the clinical site for processing and storage via a secure, refrigerated container. In the situation where a local General Practitioner (GP) practice is being utilised by the hospital clinical site for study visits (including vaccine administration) the transport of study vaccine and human specimens between the hospital clinical site to the GP practice will be completed using measures to guarantee appropriate temperature control and documented standard practices. Following administration, used study vaccine syringes will be placed immediately into locked containers or sealed bags, returned for safe storage at the hospital clinical site and retained for accountability.

All clinical site personnel involved in the handling or administration of study vaccine will be trained according to the study protocol, and all supportive documentation, including study specific laboratory and clinical trial material manuals. A thorough study-specific training will occur prior to the initiation of the study via a formal local investigator meeting and/or on-site study initiation visit.

Clinical site staff with the responsibility of administering MEDI-534, collection of serum and nasal wash specimens, or the clinical evaluation of study subjects are instructed to follow the World Health Organization (WHO) universal precautions for the prevention of transmission of infectious agents in healthcare settings (WHO Standard Precautions 2006). Clinical site staff should remember that children presenting for illness visits might be infected with wild-type respiratory viruses, and appropriate infection.

It is not anticipated that the study vaccine or any waste associated with study procedures will affect the surrounding ecosystem or environment.

All components of MEDI-534 come from viruses that are common throughout the world and all people are serially exposed to RSV and PIV3 on an annual basis.

B. Information relating to the recipient or parental organism from which the GMO is derived

1. Recipient or parental organism characterisation:

(a) Indicate whether the recipient or parental organism is a:

(select one only)

viroid	(.)
RNA virus	X
DNA virus	(.)
bacterium	(.)
fungus	(.)
animal	
- mammals	(.)
- insect	(.)
- fish	(.)
- other animal	(.)
(specify phylum, class)	…

other, specify …

2. Name

(i)	Recipient Virus	Bovine Parainfluenza Virus Type 3
(ii)	order and/or higher taxon (for animals)	Paramyxoviridae family
(iii)	genus	Respirovirus
(iv)	species	Not applicable
(v)	subspecies	Not applicable
(vi)	strain	bPIV3/15626/84

(vii)	pathovar (biotype, ecotype, race, etc.)	Not applicable
(viii)	common name	bPIV3

3. Geographical distribution of the organism

(a) Indigenous to, or otherwise established in, the country where the notification is made:

Yes X No (.) Not known (.)

(b) Indigenous to, or otherwise established in, other EC countries:

(i) Yes X

If yes, indicate the type of ecosystem in which it is found:

Atlantic	X
Mediteranean	X
Boreal	..
Alpine	..
Continental	X.
Macaronesian	..
Arctic	X

(ii) No (.)

(iii) Not known (.)

(c) Is it frequently used in the country where the notification is made?

Yes X No (.)

(d) Is it frequently kept in the country where the notification is made?

Yes X No (.)

4. Natural habitat of the organism

(a) If the organism is a microorganism

water	X
soil, free-living	X
soil in association with plant-root systems	X
in association with plant leaf/stem systems	X
other, specify	in association with animals

(b) If the organism is an animal: natural habitat or usual agroecosystem:

Not applicable

5. (a) Detection techniques
Isolation by culture
Fluorescent focus assay (FFA) to measure titers of infectious virus
Sequence analysis (PCR)

(b) Identification techniques
Reverse-Transcriptase Polymerase Chain Reaction (RT-PCR) using virus-specific
primers

6. Is the recipient organism classified under existing Community rules relating to the protection of human health and/or the environment?
Yes X No (.)
If yes, specify
ACDP Classification 1

7. Is the recipient organism significantly pathogenic or harmful in any other way (including its extracellular products), either living or dead?
Yes X No (.) Not known (.)

If yes:

(a) to which of the following organisms:

humans	(.)
animals	X
plants	(.)
other	(.)

(b) give the relevant information specified under Annex III A, point II. (A)(11)(d) of Directive 2001/18/EC

Pathogenicity, Infectivity and Host Range of bPIV3

Bovine PIV3, the plasmid backbone of MEDI-534, is transmitted through the mucous membranes of the eyes, mouth, or nose. The bPIV3 strain used in the MEDI-534 vaccine naturally occurs in cows and causes respiratory disease in calves.

Nonclinical and Clinical Studies with bPIV3

Bovine PIV3 has restricted replication in rhesus monkeys and chimpanzees (Coelingh 1988, Skiadopoulos 2003). Studies of bPIV3 in adults, children, and infants demonstrated that bPIV3 is attenuated in humans (Clements 1991, Karron 1995, Karron 1996, Greenberg 2005. bPIV3 was evaluated in a series of clinical studies and results demonstrated the safety,

tolerability, and immunogenicity of the bPIV3 virus in humans and suggested that it could be used as a vector for delivering hPIV3 and hRSV antigens for immunization of hPIV3 and RSV naive subjects. Subsequent studies evaluated administration of the bPIV3 vaccine also demonstrated that the vaccine was generally safe and well tolerated. These clinical studies demonstrated the safety and tolerability of bPIV3 in adults, children and infants as young as 2 months old. There are no reported cases of bPIV3 transmission to humans in nature. There are also no reported cases of bPIV3 transmission to plants and it is doubtful that an animal virus could initiate an infection in plant cells. bPIV3 is an animal virus and requires live animal cells for replication. It is transmitted by close contact and is inactivated by high temperature and changes in pH when exposed to the environment.

8. Information concerning reproduction

(a) Generation time in natural ecosystems:
Bovine PIV3 is a live virus which does not persist in the environment. It can only remain infectious outside a host cell for less than 8 hours and is rapidly inactivated by sunlight, heat and pH changes.

(b) Generation time in the ecosystem where the release will take place:
No laboratory manipulation or manufacture of the vaccine will take place at the clinical sites. All vaccine will be administered to subjects within the designated clinical sites, which are healthcare facilities.

(c) Way of reproduction: Sexual .. Asexual X other viral reproduction

(c) Factors affecting reproduction:
Bovine PIV3 is a live virus which requires a host cell for replication.

9. Survivability

(a) ability to form structures enhancing survival or dormancy:

(i)	endospores	(.)
(ii)	cysts	(.)
(iii)	sclerotia	(.)
(iv)	asexual spores (fungi)	(.)
(v)	sexual spores (funghi)	(.)
(vi)	eggs	(.)
(vii)	pupae	(.)
(viii)	larvae	(.)
(ix)	other, specify	None

(b) relevant factors affecting survivability:
bPIV3 requires the presence of a suitable host cell for replication and survival. bPIV3 is susceptible to environmental factors such as UV light and temperature, is susceptible to common disinfectants and will not survive for more than 8 hours at room temperature outside of a host cell.

10. (a) Ways of dissemination
As with other respiratory viruses, bPIV3 is transmitted through direct contact with infected animals or indirect contact with contaminated surfaces or objects. Infection can occur through the mucous membranes of the eyes, mouth, or nose.

(b) Factors affecting dissemination
bPIV3 is susceptible to environmental factors such as sunlight, temperature and also common disinfectants.

11. Previous genetic modifications of the recipient or parental organism already notified for release in the country where the notification is made (give notification numbers)
None

C. **Information relating to the genetic modification**

1. Type of the genetic modification

(i)	insertion of genetic material	X
(ii)	deletion of genetic material	X
(iii)	base substitution	(.)
(iv)	cell fusion	(.)
(v)	others, specify …	

2. Intended outcome of the genetic modification
MEDI-534 is a chimeric vaccine which expresses hPIV3 fusion protein (F) and hemagglutinin-neuraminidase (HN) in a bPIV3 viral backbone. In addition, the human RSV fusion protein (RSV F) has been engineered into position 2 of the genome. Therefore, the bPIV3 backbone of the vaccine is used to deliver antigens thought to be protective against both RSV and hPIV3 infection.

3. (a) Has a vector been used in the process of modification?
Yes (.) No X

If no, go straight to question 5.

(b) If yes, is the vector wholly or partially present in the modified organism?

Yes (.) No (.)

If no, go straight to question 5.

4. If the answer to 3(b) is yes, supply the following information

(a) Type of vector

plasmid	(.)
bacteriophage	(.)
virus	(.)
cosmid	(.)
transposable element	(.)
other, specify	…

(b) Identity of the vector
…

(c) Host range of the vector
…

(d) Presence in the vector of sequences giving a selectable or identifiable phenotype

Yes (.) No (.)

antibiotic resistance	(.)
other, specify	…

Indication of which antibiotic resistance gene is inserted
…

(e) Constituent fragments of the vector
…

(f) Method for introducing the vector into the recipient organism

(i)	transformation	(.)
(ii)	electroporation	(.)
(iii)	macroinjection	(.)
(iv)	microinjection	(.)
(v)	infection	(.)
(vi)	other, specify	…

5. If the answer to question B.3(a) and (b) is no, what was the method used in the process of modification?

(i) transformation (.)
(ii) microinjection (.)
(iii) microencapsulation (.)
(iv) macroinjection (.)
(v) other, specify Transfection by electroporation

6. Composition of the insert

(a) Composition of the insert
MEDI-534 is a chimeric vaccine which expresses hPIV3 fusion protein (F) and hemagglutinin-neuraminidase (HN) in a bovine PIV3 (bPIV3) viral backbone. In addition, the human RSV fusion protein (RSV F) has been engineered into position 2 of the genome.

(b) Source of each constituent part of the insert
bPIV3: PIV3/Kansas/15626/84 strain
hPIV3: Texas/12084/1983 strain
RSV: A2 strain

(c) Intended function of each constituent part of the insert in the GMO
RSV F protein
The RSV fusion (F) protein is a viral surface glycoprotein. It plays a role in cell penetration by the virus and promotes cell to cell spread through the formation of syncytia The F protein is highly conserved between RSV groups (A and B strains). It is also one of the only two RSV components that induce RSV neutralizing antibody and therefore, is an important target of RSV vaccine development.

Human PIV3 HN and F Proteins
The human PIV3 hemagglutinin-neuraminidase (HN) protein binds to sialic acid-containing receptors on host cell surfaces, and the fusion (F) protein is involved in the fusion of the viral membrane with the cellular plasma membrane. The F and HN proteins are the only PIV3 antigens that induce neutralizing antibodies, and are important targets of vaccine development for prevention of hPIV3 infection.

(d) Location of the insert in the host organism

- on a free plasmid (.)
- integrated in the chromosome X
- other, specify …

(e) Does the insert contain parts whose product or function are not known?
Yes (.) No X
If yes, specify …

D. Information on the organism(s) from which the insert is derived

1. Indicate whether it is a:

viroid (.)
RNA virus X
DNA virus (.)
bacterium (.)
fungus (.)
animal
- mammals (.)
- insect (.)
- fish (.)
- other animal (.)
(specify phylum, class) …

other, specify …

2. Complete name

(i) order and/or higher taxon (for animals) …
(ii) family name for plants …
(iii) genus …
(iv) species …
(v) subspecies …
(vi) strain …
(vii) cultivar/breeding line …
(viii) pathovar …
(ix) common name …

Donor Viruses of Inserts

	Human Parainfluenza Virus Type 3	**Respiratory Syncytial virus**
Order and/or higher taxon	Paramyxoviridae family	Paramyxoviridae family
Genus	Respirovirus	Pneumovirus
Species	Not applicable	Not applicable
Subspecies	Not applicable	Not applicable
Strain	Texas/12084/1983	A2
Pathovar	Not applicable	Not applicable
Common name	hPIV3	RSV

3. Is the organism significantly pathogenic or harmful in any other way (including its extracellular products), either living or dead?

Yes X No (.) Not known (.)

RSV and hPIV3 both cause respiratory disease in humans; however, only the HN and F (hPIV3) and F (RSV) genes of these organisms are included in the MEDI-534 vaccine.

If yes, specify the following:

(b) to which of the following organisms:

humans	X
animals	(.)
plants	(.)
other	..

(b) are the donated sequences involved in any way to the pathogenic or harmful properties of the organism

Yes X No (.) Not known (.)

If yes, give the relevant information under Annex III A, point II(A)(11)(d):
Although the RSV F and hPIV3 HN and F proteins are involved in host cell binding and penetration of the viruses, they have been inserted into a bPIV3 plasmid backbone within the MEDI-534 vaccine. This bPIV3 plasmid backbone vaccine has been demonstrated to be attenuated in humans due to its host range restriction as described previously in Section 7 of this application.

Infectivity of RSV and hPIV3 in Humans

Both wild-type RSV and hPIV3 are transmitted through direct contact with respiratory secretions of an infected individual or can be transmitted through fomites. Infection can occur when infectious material contacts mucous membranes of the eyes. Both RSV and hPIV3 are ubiquitous and all individuals can expect to be serially exposed to both viruses throughout life.

Virulence of RSV and hPIV3 in Humans

RSV is an important respiratory pathogen of infants and young children, causing annual epidemics of bronchiolitis and pneumonia worldwide. Severe RSV illness commonly occurs among infants with primary infection in the first year of life. RSV is estimated to cause as

much as 90% of all childhood bronchiolitis and up to 40% of all pediatric pneumonias (Hall 2000).

hPIV3 is responsible for a spectrum of respiratory symptoms and is second only to RSV as a cause of bronchiolitis and pneumonia among infants and young children (Chanock 2001). Most children are infected with hPIV3 by 2 years of age, but because infection does not confer complete protective immunity, reinfection occurs throughout life (Glezen 1984).

Both RSV and hPIV3 are human pathogens. Non-human primates and rodents are also permissive to hRSV and hPIV3 infection. There is no evidence that RSV and PIV3 activate latent viruses (eg, proviruses) from the cellular genome following infection; RSV and PIV3 are RNA viruses that replicate in the cytoplasm and would not be expected to activate latent viruses. No evidence exists of RSV or hPIV3 being transmitted from humans to animals or vice versa. RSV and hPIV3 are human RNA viruses that are not expected to infect microbes or plant cells which lack receptors for hPIV3 and RSV F and HN proteins, which are the proteins responsible for attachment and entry into host cells.

4. Is the donor organism classified under existing Community rules relating to the protection of human health and the environment, such as Directive 90/679/EEC on the protection of workers from risks to exposure to biological agents at work?
   Yes X No (.)
   If yes, specify ACDP Classification 2

5. Do the donor and recipient organism exchange genetic material naturally?
   Yes (.) No (.) Not known (.)
   Paramyxoviruses replicate in the cell cytoplasm and do not integrate into the host genome; recombination events have not been reported in nature. There is minimal risk of gene exchange between circulating wild-type and vaccine virus (Bukreyev 2006).

E. Information relating to the genetically modified organism

1. Genetic traits and phenotypic characteristics of the recipient or parental organism which have been changed as a result of the genetic modification

   (a) is the GMO different from the recipient as far as survivability is concerned?
   Yes (.) No X Not known (.)
   Specify …

   (b) is the GMO in any way different from the recipient as far as mode and/or rate of reproduction is concerned?
   Yes (.) No (.) Unknown X
   Specify …

(c) is the GMO in any way different from the recipient as far as dissemination is concerned?

Yes (.) No (.) Not known X

Specify

While bPIV3 has been shown to be poorly transmissible in seronegative children and infants, the magnitude and duration of viral shedding of MEDI-534 in RSV and PIV3 seronegative children is still unknown.

(d) is the GMO in any way different from the recipient as far as pathogenicity is concerned?

Yes (.) No (.) Not known (.)

Specify

MEDI-534 is not expected to be more pathogenic than bPIV3. Although the exchange of bPIV3 F and HN genes for hPIV3 F and HN results in some loss of attenuation as shown by the comparative replication levels between b/h PIV3 and bPIV3, the growth of b/h PIV3 is still more restricted than that of hPIV3 in the respiratory tract of rhesus monkeys. The addition of an extra RSV F gene in the genome of b/h PIV3 further attenuates the replication of b/h PIV3 as shown by in vitro growth curves performed in MRC-5 (primary human lung cells). Furthermore, studies in normal and experimentally immunosuppressed hamsters indicate that MEDI-534 did not exhibit enhanced tissue tropism, replicating only in respiratory tissues as expected. Therefore, from a virological point of view, MEDI-534 is not more virulent than bPIV3.

The bPIV3 plasmid backbone of MEDI-534 has demonstrated attenuation in humans as outlined in 12(d) of this application. Clinical data from completed and ongoing studies with MEDI-534 (as outlined in 31 of this application) suggest that MEDI-534 has an acceptable safety profile and restricted replication in seropositive subjects. The immunogenicity, shedding, and safety profiles in the adult and seropositive paediatric population for MEDI-534 are to date similar to those previously described with bPIV3 (Clements, 1991; Karron, 1995), the parental virus from which MEDI-534 is derived. The safety profile of MEDI-534 in seronegative young children is also expected to be similar to that of bPIV3 vaccine recipients; however, evaluation of MEDI-534 in RSV and PIV3 seronegative populations is ongoing.

MEDI-534 is currently being evaluated in an on-going Phase 1 study that evaluates the safety, tolerability, immunogenicity and vaccine-like viral shedding of MEDI-534 in seronegative children 6 to <24 months of age (study MI-CP149). A preliminary blinded evaluation after 3 doses of MEDI-534 at 10^4 median tissue culture infectious dose ($TCID_{50}$) and 1 dose of 10^5 $TCID_{50}$ 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 in the 10^6 $TCID_{50}$ dose cohort within the US. The preliminary safety profile shows that the most commonly observed adverse events have thus far been runny nose/nasal congestion, cough

and irritability/fussiness. The majority of events have been graded as mild or moderate in severity. The frequency did not increase with subsequent doses or with increased dosage. There have been no vaccine-related serious adverse events to date. Safety follow-up continues and the study remains blinded.

2. Genetic stability of the genetically modified organism
Studies in cell culture and hamsters indicate that the nonessential RSV F gene is maintained without genetic alterations through multiple passages in vitro and in vivo.

3. Is the GMO significantly pathogenic or harmful in any way (including its extracellular products), either living or dead?

Yes	(.)	No	(.)	Unknown	X

(a) to which of the following organisms?

humans	X (not known)
animals	X (not known)
plants	(.)
other	…

(b) give the relevant information specified under Annex III A, point II(A)(11)(d) and II(C)(2)(i)

MEDI-534 has demonstrated attenuation properties, genetic stability and an acceptable safety profile in relevant animal models. Data from two completed clinical studies in adults and seropositive children 1-9 years of age show that MEDI-534 was safe and well tolerated and demonstrated restricted replication in seropositive subjects. MEDI-534 is also currently being evaluated in an on-going study in RSV and PIV3 seronegative children 6 to <24 months of age, and a preliminary evaluation after 2 doses at the lowest dose indicates that the vaccine was well tolerated in this population. The bPIV3 Kansas/15626/84 strain that serves as a backbone for the MEDI-534 vaccine naturally occurs in cows and has been shown to cause respiratory disease in calves. 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. MEDI-534 is capable of infecting humans, non-human primates, bovines, hamsters and neonatal ferrets, however, its replication has shown to be attenuated in humans and non-human primates due to the host range restriction of the bPIV3 backbone. No latent viruses were detected in the master virus seed used for production of MEDI-534. There is no evidence that MEDI-534 activates latent viruses (eg, proviruses) from the cellular genome following infection; bPIV3 is an RNA virus that replicates in the cytoplasm and would not be expected to activate latent viruses. No evidence exists of MEDI-534 being transmitted from humans to animals or vice versa.

ii. in relation to human health -

a. the toxic or allergenic effects of the non-viable organism and/or its metabolic products,

No MEDI-534-specific toxic effects have been observed in animal toxicity studies, and no toxic effects have been seen in any clinical studies to date. No allergenic effects have been observed in clinical studies to date.

b. the product hazards,

No product hazards are known from studies to date.

c. the comparison of the organism to the donor, recipient or (where appropriate) parental organism regarding pathogenicity,

Available immunogenicity, shedding, and safety data for MEDI-534 in adults and seropositive children are similar to those previously described with the bPIV3 viral backbone (Clements 1991, Karron 1995).

d. the capacity of the organism for colonisation, and

MEDI-534 is capable of colonizing only the respiratory tree as shown in preclinical studies.

e. if the organism is pathogenic to humans who are immunocompetent –

i. diseases caused and mechanisms of pathogenicity, including invasiveness and virulence

The bPIV3 plasmid backbone of MEDI-534 has demonstrated attenuation in humans as previously discussed. Clinical data from completed and ongoing studies with MEDI-534 suggest that it has an acceptable safety profile and restricted replication in seropositive subjects. The safety profile of MEDI-534 in seronegative young children is also expected to be similar to that of bPIV3 vaccine recipients; however, evaluation of MEDI-534 in RSV and PIV3 seronegative populations is ongoing.

ii. communicability

MEDI-534 is a live viral vaccine, and replication of the vaccine virus 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. Transmissibility of the live bPIV3 vaccine (the backbone of MEDI-534) has been previously evaluated and was shown to be poorly transmissible in infants and children (Karron, 1995). Although viral shedding of MEDI-534 has been shown to be 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. The study exclusion criteria outlined in the protocol excludes 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. The attenuation characteristics and initial safety profile of MEDI-534 lead us to conclude that any risks of exposure will be no greater than of wild-type

RSV/PIV3 to which all children are serially exposed. Viral shedding of MEDI-534 during the study will also be monitored through the collection of nasal wash specimens at defined intervals.

iii. infective dose

The proposed study is a dose escalation study that will determine the infective dose. Doses of up to 10^6 $TCID_{50}$ have been demonstrated to be minimally infective in seropositive adults and children.

iv. host range and possibility of alteration

MEDI-534 is capable of infecting humans, non-human primates, bovines, hamsters and neonatal ferrets, however, it has shown to be attenuated in humans and non-human primates due to the host range restriction of the bPIV3 backbone. 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).

v. possibility of survival outside of human host

MEDI-534 can not survive in the environment without a host cell. It is susceptible to common disinfectants and cleaning agents. As a live virus, it also requires a host cell for replication. The virus would not be viable after 8 hours at room temperature without a host cell, while other factors such as sunlight, heat and pH changes will further diminish its chance of survival outside a host.

vi. presence of vectors or means of dissemination

MEDI-534, like wild-type RSV and PIV3, is transmitted through direct contact with respiratory secretions of an infected individual or indirectly through fomites. Infection can occur when infectious material contacts mucous membranes of the eyes, mouth, or nose.

vii. biological stability

MEDI-534 is designed to elicit an immune response to hPIV3 and hRSV. It is unknown how long lasting these responses will be. The virus itself should be cleared after approximately 10 days based on previous shedding data from clinical studies of bPIV3 (Karron 1995, Karron 1996).

viii. antibiotic-resistance patterns

MEDI-534 is not resistant to antibiotics because it is a virus.

ix. allergenicity, and

MEDI-534 has not been shown to be allergenic in any preclinical or clinical studies to date.

x. availability of appropriate therapies

Currently no vaccine exists for the prevention of RSV or hPIV3 infections and disease. Aerosolised ribavirin is used as a treatment for hospitalized infants and young children below 2 years of age with acute lower respiratory tract illness due to RSV. Palivizumab (Synagis) is prescribed prophylactically to premature and other high-risk infants to prevent serious RSV disease.

4. Description of identification and detection methods

(a) Techniques used to detect the GMO in the environment
Nasal wash specimens will be collected from study participants to assess vaccine virus replication and viral shedding. …

(b) Techniques used to identify the GMO

The vector is identified by the presence of the hPIV3 F and bPIV3 M gene junctions. The RSVF insert is identified by RT-PCR.

F. Information relating to the release

1. Purpose of the release (including any significant potential environmental benefits that may be expected)
MEDI-534 is a live, attenuated intranasal vaccine being investigated for the prevention of lower respiratory tract illness caused by respiratory syncytial virus (RSV) and parainfluenza virus type 3 (PIV3) in young infants. This study is being conducted to evaluate the safety and immune response of this vaccine in healthy 6 to <24 month-old children and in 2 month-old infants. …

2. Is the site of the release different from the natural habitat or from the ecosystem in which the recipient or parental organism is regularly used, kept or found?
Yes (.) No X
If yes, specify …

3. Information concerning the release and the surrounding area
(a) Geographical location (administrative region and where appropriate grid reference):

The study vaccine will be administered at healthcare facilities where paediatric immunizations are commonly administered. Additionally, the study protocol provisions for some post-dosing study visits to be conducted in the home of subjects. In-home visits will be conducted by qualified and trained site personnel. The visit will consist of a clinical evaluation of the study subject, as well as the collection of human specimens (nasal wash and serum samples). Specimens obtained in the home will be collected according to the study-specific laboratory manual and promptly transported to the clinical site for processing and storage via a secure, refrigerated container.
The following are clinical study sites within England where study vaccine will be administered:

Site 1
The GMO will be administered at the Bristol Royal Hospital for Children, Paul O'Gorman Building, Upper Maudlin Street, Bristol, BS2 8BJ, United Kingdom.

Site 2
The GMO will be administered at the Sheffield Children's Hospital, Western Bank, Sheffield, S10 2TH, United Kingdom.

Site 3
The GMO will be administered at the Leeds General Infirmary, Claredon wing, Belmont Grove, Leeds, LS2 9NS, United Kingdom.

Site 4
The GMO will be administered at the Wellcome Trust Clinical Facility, University of Southampton, Southampton University Hospitals NHS Trust, Southampton, SO16 6YD, United Kingdom.

Site 5
The GMO will be administered at the Alder Hey Children's Hospital NHS FT, Eaton Road, Alder Hey, Liverpool, L12 2AP, United Kingdom.

Site 6
The GMO will be administered at the Royal Devon and Exeter NHS Foundation Trust, Child Health Building, Barrack Road, Exeter, EX2 5DW, United Kingdom.

Site 7
The GMO will be administered at the Division of Child Health, St.George's University of London, Cranmer Terrace, London, SW17 0RE, United Kingdom.

Site 8
The GMO will be administered at the Centre for Clinical Vaccinology and Tropical Medicine, Churchill Hospital, Old Road, Headington, Oxford, OX3 7LJ, United Kingdom.

Site 9
The GMO will be administered at the Seacroft Hospital, York Road, Leeds, West Yorkshire, LS14 6UH, United Kingdom.

Site 10
The GMO will be administered at the Southfields Group Practice, 492 Merton Road, Wandsworth, London, SW18 5AE, United Kingdom.

(b) Size of the site (m^2):
- (i) actual release site (m^2): not applicable
- (ii) wider release site (m^2): not applicable

(c) Proximity to internationally recognised biotopes or protected areas (including drinking water reservoirs), which could be affected:

The study vaccine will be administered 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.

(d) Flora and fauna including crops, livestock and migratory species which may potentially interact with the GMO
The bPIV3 Kansas/15626/84 strain that serves as a backbone for the MEDI-534 vaccine naturally occurs in cows and has been shown to cause respiratory disease in calves. 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.

4. Method and amount of release

(a) Quantities of GMOs to be released:
It is estimated that a total of 120 MEDI-534 kits (360 total 0.2 ml syringes) and 120 Placebo kits (360 total 0.2 ml syringes) will be distributed to clinical sites in England

(b) Duration of the operation:
Enrolment in the EU began in April 2009 and is anticipated to be completed by March 2012.

(c) Methods and procedures to avoid and/or minimise the spread of the GMOs beyond the site of the release
Procedures are in place for transport to and from and storage at clinical sites, administration of the vaccine and clinical sample collections, waste handling, and monitoring of viral shedding from study subjects during the trial. These procedures contain the appropriate measures to avoid the spread of the MEDI-534 vaccine in the environment.

5. Short description of average environmental conditions (weather, temperature, etc.)
England has a climate with warm to hot summers and colder, wetter winters.

6. Relevant data regarding previous releases carried out with the same GMO, if any, specially related to the potential environmental and human health impacts from the release.

Overview of Results from Previous Releases of MEDI-534

MEDI-534 (the GMO) has been evaluated in two completed and one ongoing Phase 1 studies within the United States. Additionally, an international Phase1/2a study has been launched in

children 2-24 months of age, and enrollment has been initiated in the United States. A list and description of these studies is provided in Table 1. Study MI-CP119 was a Phase 1 study performed to evaluate the safety and tolerability of MEDI-534 in healthy adults. Study MI-CP130 was a Phase 1 study performed to evaluate the safety and tolerability of MEDI-534 in healthy RSV and PIV3 seropositive children 1 to 9 years of age. MEDI-534 is also being evaluated in an ongoing Phase 1 study (MI-CP149) to evaluate the safety, tolerability, immunogenicity and vaccine shedding in seronegative children 6 to <24 months of age. All of these studies have been/are being conducted within the United States under an Investigational New Drug Application (IND). MEDI-534 has not yet been released outside of the United States.

In these studies, MEDI-534 was administered intranasally to healthy adults, children, and infants. Previous and ongoing clinical studies with MEDI-534 are designed to assess safety, viral shedding, and immunogenicity of this potential vaccine candidate against infection with respiratory syncytial virus (RSV) and parainfluenza virus type 3 (PIV3). These respiratory viruses are spread via large respiratory droplets. Close contact is required for transmission. Both RSV and hPIV3 are ubiquitous in the general population and all individuals can expect to be serially exposed to both viruses throughout life.

Overall, the data from clinical testing in healthy adults and seropositive children 1 to 9 years of age (study MI-CP119 and study MI-CP130, respectively) suggest that MEDI-534 has an acceptable safety profile and restricted replication in seropositive subjects. The immunogenicity, shedding, and safety profiles in the adult and seropositive paediatric population are similar to those previously described with bPIV3 (Clements, 1991; Karron, 1995), the parental virus from which MEDI-534 is derived. The safety profile of MEDI-534 in seronegative young children is also expected to be similar to that of bPIV3 vaccine recipients.

Adverse events included minor reactogenicity events of the upper respiratory tract such as runny nose/nasal congestion, sore throat, and cough. Delivery by an intranasal route of administration may result in epistaxis. Epistaxis was reported in two children (MEDI-534 vs placebo, p=0.49) who received the highest dose (10^6 $TCID_{50}$) of MEDI-534 in Study MI-CP130, and subjects may be at increased risk for developing this adverse event. Systemic symptoms related to low-grade viral illness may potentially be observed and include fever, chills or feverishness, muscle aches, and fatigue (malaise/lethargy). Some respiratory viruses are known to precipitate wheezing illnesses, including asthma exacerbations. Wheezing was observed in two adults who received MEDI-534 in Study MI-CP119. No wheezing events were observed in MEDI-534 recipients during clinical testing in seropositive RSV and PIV3 paediatric populations in Study MI-CP130. Whether MEDI-534 will be associated with an increased risk of wheezing in seronegative RSV and PIV3 children is unknown.

Natural infection with both RSV and PIV3 in young children can result in significant lower respiratory tract infections, including pneumonia, bronchitis, bronchiolitis, croup, and upper respiratory tract infections that can be complicated with acute otitis media. Acute otitis

media was diagnosed in two children (p=0.49) who received the highest dose (10^6 $TCID_{50}$) of MEDI-534 in Study MI-CP130 and subjects may be at increased risk for developing this adverse event.

Table 1 Summary of MEDI-534 Clinical Studies

Study	Primary Objectives	Design	Population	Route	Dosing Schedule	Dosage	Enrolled/ Planned [a]	Study Status [a]
MI-CP119	Safety Tolerability	Phase 1 Randomized Double-blind Placebo-controlled Dose-escalation	Healthy adults 18-40 years of age	Intranasal	Single dose	10^4 $TCID_{50}$ [b] 10^5 $TCID_{50}$ 10^6 $TCID_{50}$	120/120	Completed/ CSR submitted to FDA
MI-CP130	Safety Tolerability	Phase 1 Randomized Double-blind Placebo-controlled Dose-escalation	Healthy 1 to 9 year-old RSV and PIV3 seropositive children	Intranasal	Single dose	10^4 $TCID_{50}$ 10^5 $TCID_{50}$ 10^6 $TCID_{50}$	120/120	Completed/ CSR submitted to FDA
MI-CP149	Safety Tolerability	Phase 1 Randomized Double-blind Placebo-controlled Dose-escalation	Healthy 6 to <24 month-old RSV and PIV3 seronegative children	Intranasal	Three doses at 0, 2 and 4 months	10^4 $TCID_{50}$ 10^5 $TCID_{50}$ 10^6 $TCID_{50}$	40/49	Ongoing

Table 1 Summary of MEDI-534 Clinical Studies

Study	Primary Objectives	Design	Population	Route	Dosing Schedule	Dosage	Enrolled/ Planned [a]	Study Status [a]
MI-CP178	Safety Tolerability	Phase 1/2a Randomized Double-blind Placebo-controlled Dose-escalation	Healthy 6 to <24 month-old RSV and PIV3 seronegative children and unscreened 2 month-old infants	Intranasal	Three doses at 0, 2 and 4 months	6 to <24 month-old children: 10^5 $TCID_{50}$ 10^6 $TCID_{50}$ 2 month-old infants: 10^4 $TCID_{50}$ 10^5 $TCID_{50}$ 10^6 $TCID_{50}$	34/720	Ongoing

[a] Enrollment and study status as of 13Apr2009

[b] TCID50 = median tissue culture infectious dose

Study MI-CP178 is being conducted to evaluate 10^5 and 10^6 $TCID_{50}$ dosages of MEDI-534 in additional RSV and hPIV3 seronegative children 6 to < 24 months of age to expand the safety database. Additionally, dosages of 10^4, 10^5 and 10^6 $TCID_{50}$ will be studied in unscreened infants 2 months ± 4 weeks of age to assess safety, immunogenicity and vaccine shedding in the young infants who are the target population for an RSV and hPIV3 vaccine. Enrollment in MI-CP178 has been initiated in the United States and is anticipated to begin in Europe during April 2009.

Viral Shedding of MEDI-534

Replication of MEDI-534 in the nasal mucosa is required to generate an immune response. Shedding of vaccine virus constitutes release of the GMO. It is expected that RSV and PIV3 naïve recipients may shed vaccine virus through nasal secretions. MEDI-534 has been tested in animal models and humans and has been found to have an acceptable safety profile and restricted replication in seropositive subjects.

Shedding of MEDI-534 was previously evaluated in two clinical studies conducted in healthy adults (Study MI-CP119) and in seropositive children (Study MI-CP130). In both studies nasal wash specimens were collected at days 3, 7, 14, and 28-42 after dosing. In adults, shedding of MEDI-534 was detected in 1.6% (1 out of 60) of vaccinees and was detected at Day 3 after vaccination only. The subject was asymptomatic, and the virus was present at such low levels that its titer could not be quantified. In RSV and PIV3 seropositive adults previous exposure limits viral replication, and wild-type disease is limited to upper respiratory tract symptoms. MEDI-534 is significantly more attenuated than wild-type RSV and hPIV3, and replication is extremely limited even when high titer vaccine is delivered directly into the nose. In seropositive 1-9 year old children, no shedding was detected after receiving MEDI-534 at doses of 10^4 to 10^6 $TCID_{50.}$ The duration of viral shedding for MEDI-534 in RSV and PIV3 seronegative children is still unknown, however available data from a PIV3 seronegative population administered with the bPIV3 vaccine (the viral backbone of MEDI-534) indicates that the mean number of days of vaccine virus shedding in subjects receiving a 10^5 $TCID_{50}$ dose of vaccine ranged from 10.4 to 10.7 days (Karron 1995, Karron 1996), and that the percentage of subjects experiencing vaccine virus shedding decreased with administration of subsequent doses of vaccine (Karron 1995, Greenberg 2005). This duration of shedding is consistent with other attenuated intranasal RSV and PIV3 vaccines (Karron 1995, Karron 2005).
Although viral shedding of MEDI-534 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. Both RSV and hPIV3 are ubiquitous in the general population and all individuals can expect to be serially exposed to both viruses throughout life. Therefore, it is unlikely that a risk exists for exposure to the general population. Shedding of MEDI-534 leading to secondary transmission to vulnerable populations such as pregnant women, immunocompromised individuals, and seronegative children is possible.

Risk Management Procedures To Be Utilized in Study MI-CP178

As with the previously conducted MEDI-534 studies conducted in the United States, potential risks for this study will be managed through several avenues:

This study will be conducted in accordance with the United States Code of Federal Regulations and ICH guidelines.

- 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 according to the guidelines outlined in International Conference on Harmonisation (ICH) E6 - Good Clinical Practices. 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, processing and storage of human specimens (nasal wash and serum samples);

- All clinical sites will be regularly monitored by MedImmune (or its designee) for protocol adherence and compliance with all applicable regulations and guidelines.

Clinical site staff will be thoroughly trained on the study protocol prior to initiation of the study.

- A thorough study-specific training covering all aspects of the study will occur prior to the initiation of the study via a formal local investigator meeting and/or on-site study initiation visit. All clinical site personnel involved in the handling or administration of the GMO will be trained according to the study protocol, and all supportive documentation, including study specific laboratory and clinical trial material manuals;
- MEDI-534 vaccine is classified as a Biosafety Level 1 organism for practices involving biological materials and containment facilities (as defined by the United States Center for Disease Control and Prevention, Laboratory Biosafety Level Criteria), and requires no additional training for handling at a clinical study site or administration to subjects. Thus, standard universal precautions as dictated by the WHO (WHO 2006) are adequate in dealings with MEDI-534 and should be followed at any clinical trial site in accordance to ICH/GCP;
- Clinical site staff with the responsibility of administering MEDI-534, collection of serum and nasal wash specimens, or the clinical evaluation of study subjects are instructed to follow the World Health Organization (WHO) universal precautions for the prevention of transmission of infectious agents in healthcare settings (WHO Standard Precautions 2006). Clinical site staff should remember that children presenting for illness visits might be infected with wild-type respiratory viruses, and appropriate infection control practices should be used. Based on its attenuation profile in animal models as well as in adults and seropositive children, the risk of transmission and illness is lower for MEDI-534 than for commonly circulating respiratory viruses;
- All transport of MEDI-534 will be done so according to guidelines for the transport of GMOs and IATA Transportation Regulations;
- Study vaccine will be stored at -60°C or below in the original outer package and will be stored in a secure location with limited access. Following administration, used study vaccine syringes will be placed immediately into locked containers or sealed bags and retained for accountability. Upon reconciliation and accountability, used study vaccine syringes will be destroyed by the clinical site following institutional procedures for the disposal of biohazardous material. All unused study vaccine will be returned to MedImmune's central storage depot in Europe or disposed of at the clinical site upon authorization of MedImmune. MEDI-534 should be discarded as "biohazardous waste (a.k.a. "medical waste") or, alternatively, decontamination of waste can be performed by steam sterilization for 30 minutes at 121°C.

Only subjects meeting all protocol-defined eligibility criteria will be enrolled into the study.

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. The exclusion criteria provide a

guideline for the extent of contact that should be avoided to minimize the risk of transmission to these populations and include:

- Expected to be living in the same home or enrolled in the same classroom at day care with infants <6 months within 28 days after each dose;
- Expected contact with a pregnant caregiver within 28 days after each dose;
- A household contact who is immunocompromised; the subject should also avoid close contact with immunocompromised individuals for at least 28 days after any study vaccine dose;
- Expected household contact within 28 days after each dose with a health care provider for immunocompromised patients or who is a day care provider for infants under the age of 6 months.

Detailed safety monitoring of all enrolled subjects, including viral shedding

- Subjects will be observed for a minimum of 30 minutes after administration of each dose of MEDI-534. Emergency supplies (e.g., AMBU bag, adrenaline, antihistamine) will be available for the initial treatment of an allergic reaction, if required;
- Subjects will have 3 scheduled visits after each dose (Days 7, 12, and 28) for the collection of nasal wash specimens to be used in the assessment of viral shedding of MEDI-534. Additionally, subjects will be required to arrange an unscheduled visit for medical evaluation and nasal wash collection based on illness criteria as defined in the study protocol to assess viral shedding with concurrent illness;
- The legal representative(s) for enrolled subjects will be provided a digital rectal/axillary thermometer and will maintain a daily diary of symptoms (including body temperatures) and medications/immunizations received for the 28 days after each dose of MEDI-534;
- As natural infection with both RSV and PIV3 in young children can result in lower respiratory tract infections, including pneumonia, bronchitis, bronchiolitis, and croup, clinical sites will be actively monitoring for the occurrence of MA-LRI (including wheezing, bronchiolitis, croup, pneumonia, bronchitis, apnea, rales, and rhonchi) through the entire duration of the study. Upon becoming aware of these events, clinical sites will be required to report them to MedImmune product safety within 24 hours. This will allow MedImmune to assess the occurrence of MA-LRI throughout the study on a real-time basis with regards to pre-defined stopping rules as specified in the study protocol;
- All subjects will be followed for a total of 365 days (1 year) from receipt of first dose of study vaccine to allow for all subjects to be followed for safety when RSV circulates irrespective of local epidemiology. The legal representative(s) for enrolled subjects will be contacted by phone on a monthly basis after the last clinic visit at 28 days post dose 3 through the end of the study.

The MedImmune Medical Monitor will review in real time all events defined in the study protocol as Immediately Reportable Events (IREs), as well as any other significant adverse events reported to MedImmune.

- An electronic data capture (EDC) will be employed on this study for the collection of data from clinical sites. Implementation of EDC will expedite the collection and review of safety data;
- Per the study protocol, serious adverse events (SAE), Medically Attended Lower Respiratory Illness (MA-LRI) and grade 3/4 adverse events (AE) must be reported to

MedImmune product safety within 24 hours of the clinical site becoming aware of the event.

In additional to the Medical Monitor, a Safety Monitoring Committee (SMC) will also share responsibility for safety management during the study.

- The SMC is composed of at least two MedImmune physicians who are not directly involved in the day-to-day operations of the study, and two physicians who are not employees of MedImmune;
- The SMC will independently review cumulative safety surveillance data, as well as review and approve the recommendations of the Medical Monitor regarding dose escalation, on a regular basis throughout the study and make further recommendations regarding conduct of the study;
- The SMC will also review safety data at other time points in response to MA-LRIs or other AEs considered medically significant by the Medical Monitor.

The study protocol (Dose interruption) outlines the events that would discontinue dosing and enrollment of additional subjects until review of the event in question by the Medical Monitor and the SMC.

The monitoring and control procedures described above provide assurance that the safety of the study subjects will be sufficiently evaluated for the duration of the study. Additionally, collection of nasal wash specimens at defined intervals during the study ensures that monitoring of viral shedding, and thus, monitoring of the release of the GMO, is appropriately assessed.

G. Interactions of the GMO with the environment and potential impact on the environment, if significantly different from the recipient or parent organism

1. Name of target organism (if applicable)

(i)	order and/or higher taxon (for animals)	Primates
(ii)	family name for plants	…
(iii)	genus	*Homo*
(iv)	species	*Homo sapiens*
(v)	subspecies	Not applicable
(vi)	strain	Not applicable
(vii)	cultivar/breeding line	Not applicable
(viii)	pathovar	Not applicable
(ix)	common name	human

2. Anticipated mechanism and result of interaction between the released GMOs and the target organism (if applicable)

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 of natural infection by replication in the nasal passages.

3. Any other potentially significant interactions with other organisms in the environment
None

4. Is post-release selection such as increased competitiveness, increased invasiveness for the GMO likely to occur?
Yes (.) No X Not known (.)
Give details
…

5. Types of ecosystems to which the GMO could be disseminated from the site of release and in which it could become established
MEDI-534 is labile and does not survive outside of a host cell at room temperature for more than 8 hours. The study will be conducted at standard healthcare facilities and administration will be performed intranasally directly into the study subject. It is therefore not anticipated that the study vaccine or any waste associated with study procedures will be distributed to or affect the surrounding ecosystem.

6. Complete name of non-target organisms which (taking into account the nature of the receiving environment) may be unintentionally significantly harmed by the release of the GMO

(i)	order and/or higher taxon (for animals)	Bovidae
(ii)	family name for plants	*Bos*
(iii)	genus	*taurus*
(iv)	species	Not applicable
(v)	subspecies	Not applicable
(vi)	strain	Not applicable
(vii)	cultivar/breeding line	Not applicable
(viii)	pathovar	Not applicable
(ix)	common name	cow

7. Likelihood of genetic exchange in vivo

(a) from the GMO to other organisms in the release ecosystem:
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).

(b) from other organisms to the GMO:
See 7a above

(c) likely consequences of gene transfer:

Paramyxoviruses replicate in the cell cytoplasm and do not integrate into the host genome. 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). 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.

8. Give references to relevant results (if available) from studies of the behaviour and characteristics of the GMO and its ecological impact carried out in stimulated natural environments (e.g. microcosms, etc.):
No studies have been conducted on the ecological impact of MEDI-534 on simulated natural environments.

9. Possible environmentally significant interactions with biogeochemical processes (if different from the recipient or parental organism)

There is no evidence to suggest that MEDI-534 will have any impact on agricultural production, general ecology, environmental quality and pollution in the area of release. MEDI-534 is not an agriculture genetically modified organism. It is an RNA animal virus that replicates in mammalian cells. MEDI-534 cannot infect microbes and plant cells which lack receptors for hPIV3F and HN proteins, which are the proteins responsible for attachment and entry of MEDI-534 into host cells. MEDI-534 does not persist in the environment. It can only remain infectious outside a host cell for no more than 8 hours and is rapidly inactivated by UV, heat and pH changes. It is susceptible to common disinfectants and cleaning agent, such as 1% sodium hypochlorite, 70% ethanol, 2% glutaraldehyde and detergents.

Bovine PIV3 (the backbone for MEDI-534) is antigenically related to hPIV3 but is not virulent in humans. The bPIV3 Kansas/15626/84 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. The bPIV3 infection on its own is usually uncomplicated and subclinical, associated with mild clinical illness only. In a clinical study, 3-week-old calves were directly challenged with bPIV3 and developed only very mild clinical signs (Vangeel 2007). However, under natural conditions, bPIV3 infection is usually accompanied by infection with other respiratory viruses, bacteria and/or mycoplasmas. It is believed that bPIV3 plays a significant role in the bovine respiratory disease complex by predisposing the respiratory tract of cattle to secondary infections (Todd 1975).

H. Information relating to monitoring

1. Methods for monitoring the GMOs

The study will be monitored by MedImmune or its designee on a regular basis throughout the study period in accordance with general monitoring principles set forth in ICH E5. Safety of the study subjects, including monitoring for RSV enhanced disease, will be evaluated throughout the duration of the study. Viral shedding will be evaluated during the study through the collection and evaluation of nasal wash samples. Immune response to the MEDI-534 vaccine will be assessed during the study.

2. Methods for monitoring ecosystem effects

The dissemination and impact of MEDI-534 on ecosystems is limited because dissemination requires close contact with infected nasal secretions. The study will be conducted at standard healthcare facilities where paediatric vaccines are normally administered. It is not anticipated that the study vaccine or any waste associated with study procedures will affect the surrounding ecosystem; therefore monitoring of ecosystem effects is not planned. MEDI-534 is a Biosafety Level 1 organism according to guidelines published by the United States Centers for Disease Control and Prevention (CDC), and is therefore considered to have minimal potential hazard to laboratory

personnel and the environment. Standard universal precautions that are mandated in medical facilities are adequate to prevent accidental transmission.

3. Methods for detecting transfer of the donated genetic material from the GMO to other organisms
As noted previously, there is minimal risk of gene exchange between circulating wild-type and vaccine viruses. Additionally, MEDI-534 replication and survival is reliant on appropriate host organisms. Therefore, no monitoring of other organisms is planned.

4. Size of the monitoring area (m^2)
Not applicable.

5. Duration of the monitoring
Subjects will be followed for a total of 365 days (1 year) from receipt of first dose of study vaccine

6. Frequency of the monitoring
Frequency of monitoring for safety, immunogenicity and viral shedding is detailed within the study protocol.

I. Information on post-release and waste treatment

1. Post-release treatment of the site
Clinical study sites will be instructed to follow normal site procedures for disposal of biomedical waste.

2. Post-release treatment of the GMOs

Used and unused MEDI-534 droppers will be discarded as biomedical waste and disposed of according to standard clinical site procedures.

3. (a) Type and amount of waste generated
Up to approximately 360 0.2 ml dose syringes of MEDI-534 and placebo could be generated as waste. At least two serum samples and nine nasal wash samples will be collected from each individual. In addition, medical examinations will be conducted on each subject as defined by the study protocol.

3. (b) Treatment of waste
Clinical study sites will be instructed to follow normal site procedures for disposal of biomedical waste.

J. Information on emergency response plans

1. Methods and procedures for controlling the dissemination of the GMO(s) in case of unexpected spread
Unexpected spread of MEDI-534 would be limited to accidental release of dropper contents (0.2 ml total); therefore, possibility of spread would be minimal. MEDI-534 is susceptible to common disinfectants and physical inactivation is rapidly achieved by UV irradiation and

steam sterilization. MEDI-534 does not survive outside of a host at room temperature for more than 8 hours.

2. Methods for removal of the GMO(s) of the areas potentially affected

If decontamination procedures are deemed necessary for any reason, a freshly prepared 1:10 solution of household bleach (~3.5% sodium hypochlorite) and water can be used.

3. Methods for disposal or sanitation of plants, animals, soils, etc. that could be exposed during or after the spread

Administration of MEDI-534 will occur only within contained clinical sites. It is therefore not anticipated that MEDI-534 will come into direct contact with any plants, animals or soils.

4. Plans for protecting human health and the environment in the event of an undesirable effect

As described above, extensive procedural controls are in place for the transport, storage, administration, disposal and monitoring of MEDI-534 vaccination for the duration of the clinical study. Should any unexpected undesirable effect occur, MedImmune will follow standard procedures of assessment of the effect and decisions regarding study continuance.

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