Adviesraad voor Bioveiligheid
Conseil consultatif de Biosécurité

Advice of the Belgian Biosafety Advisory Council on the notification B/BE/18/BVW2 of the Centre for the Evaluation of Vaccination (University of Antwerp) for deliberate release in the environment of genetically modified organisms other than higher plants for research and development

Adopted on 10/08/2018
Ref. SC/1510/BAC/2018_0578

Context

The notification B/BE/18/BVW2 has been submitted by the Centre for the Evaluation of Vaccination (University of Antwerp) to the Belgian Competent Authority in May 2018 for a request of deliberate release in the environment of genetically modified organisms other than higher plants for research and development according to Chapter II of the Royal Decree of 21 February 2005.

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

The dossier has been officially acknowledged by the Competent Authority on 9 May 2018 and forwarded to the Biosafety Advisory Council (BAC) for advice.
Within the framework of the evaluation procedure, the BAC, under the supervision of a coordinator and with the assistance of its Secretariat, contacted experts to evaluate the dossier. Two experts from the common list of experts drawn up by the BAC and the Service Biosafety and Biotechnology (SBB) of Sciensano answered positively to this request. The SBB also took part in the evaluation of the dossier. The Unit Transversal and applied genomics of Sciensano evaluated the analytical procedure for the detection of the two nOPV2 candidate vaccines.
The experts and the SBB assessed whether the information provided in the notification was sufficient and accurate in order to state that the deliberate release of the genetically modified organism (GMO) for its intended use, would not raise any problems for the environment, animal health or human health (people coming in contact with the treated patient and/or with the GMO). See Annex II for an overview of all the comments from the experts.

On 26 June 2018, based on a list of questions prepared by the BAC, the Competent Authority requested the notifier to provide additional information about the notification. The answers from the notifier to these questions, including additional inclusion criteria and instructions for volunteers willing to participate to the trial, were received by the Competent Authority on 24 July 2018 and transmitted to the secretariat of the BAC on the same day. This complementary information was reviewed by the coordinator and the experts.

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The scientific evaluation has been performed considering following legislation:
- Annex II (principles for the risk assessment) and annex III (information required in notifications) of the Royal Decree of 21 February 2005.
- Commission Decision 2002/623/EC of 24 July 2002 establishing guidance notes supplementing Annex II to Directive 2001/18/EC.
The pure medical aspects concerning the efficacy of the vaccine and its safety for the study subjects, as well as aspects related to social, economic or ethical considerations, are outside the scope of this evaluation.

In parallel to the scientific evaluation of the notification, the Competent Authority also made the dossier available on its website for the one-month public consultation foreseen in the abovementioned Royal Decree. The Competent Authority received several comments from the Dutch competent authorities by means of the public consultation. Comments from the Dutch GMO office (RIVM, 19/06/18) and the German Federal Office of Consumer Protection and Food Safety (BVL, 24/07/18) were also made on the Summary Notification Information Format (SNIF) on behalf of the Dutch and German Competent Authorities respectively in the frame on the European Union (EU) system of exchange of information established under Article 11 of Directive 2001/18/EC.
According to Article 16 §2 of the Royal Decree of 21 February 2005, the comments that are relevant for biosafety received in the frame of the public consultation and via the EU system of exchange of information, have been taken into account in the preparation of the advice below.

Summary of the scientific evaluation

1. The characteristics of the donor, the recipient or parental organism

The novel candidate vaccines, referred to as nOPV2 candidate vaccines, are two distinct genetically modified (GM) polioviruses derived from the Sabin oral polio vaccine type 2 vaccine (Sabin OPV2). Sabin OPV2 was one of the components of the worldwide trivalent OPV vaccination programs and was still used in most developing countries until April 2016. Sabin OPV2 is an attenuated strain of wild type poliovirus type 2 that, though its high effectiveness to interrupt the spread of the latter, has the disadvantage to have an inherent genetic instability at attenuating positions. In the human gut, Sabin OPV2 quickly presents changes rendering a RNA stem-loop structure (known as domain V structure) thermodynamically more stable, leading to reversion to a more virulent phenotype as compared to the Sabin OPV2. Sabin OPV2 vaccines have also been shown to revert to neurovirulence by recombination with specific sequences of C enteroviruses.
Polioviruses are non-enveloped viruses that can survive for weeks or months depending on environmental conditions. For example, an estimation used by WHO (2003) is an 90% decrease in infectivity every 26 days in sewage, every 5.5 days in fresh water and every 2.5 day in sea water at ambient temperature. Poliovirus do not form biological survival structures and their host range is highly restricted to humans. There is no evidence that non-primates or any other organism in nature could serve as reservoir.
Until 2001, routine and mandatory vaccination programs in Belgium involved the use of Sabin OPV2.

2. Information related to the characteristics of the GMO and the medication

Each of two nOPV2 candidate vaccines have been genetically modified i) to reduce the probability of reversion to a more neurovirulent phenotype by improving the genetic stability of the attenuated phenotype and ii) to reduce the frequency of recombination events. Briefly, the type of genetic modifications includes nucleotide substitutions, nucleotide insertion sequences into the 5'UTR regions and/or lead to codon change with or without amino acid changes. With the exception of the polymerase modifications in candidate 1 (resulting in two amino acid substitutions), all purposeful modifications are silent modifications of the RNA sequence designed to improve the stability of the attenuated phenotype. Insertion of new sequences were all produced synthetically from *in silico* designed sequences and no genetic material came from another source.

Non-clinical safety studies indicate that the nOPV2 candidate vaccines are at least as attenuated as the recipient Sabin OPV2 strain. Results obtained on shed nOPV2 candidate 1 and 2 virus from a first in human trial also show no meaningful increase in neurovirulence in the transgenic mouse model compared to the clinical trial material, in contrast to a marked loss of attenuation that would be expected from corresponding Sabin OPV2 vaccinees. Furthermore, deep sequencing results on shed virus samples support the increased genetic and phenotypic stability of the nOPV2 candidate vaccines compared to Sabin OPV2 strain as both candidates retained the deliberately introduced modifications and no changes known to be associated with reversion to neurovirulence were observed.

3. The conditions of the release

The study is planned to recruit 332 healthy volunteers, aged 15 to 50 years, of which 200 have been vaccinated with OPV and 132 with IPV. Exclusion criteria during the total duration of the study include amongst others travelling to polio endemic countries or countries with evidence of recent (within last six months) wild or vaccine-derived poliovirus circulation; professional handling of food, catering or food production activities; having household or professional contact with known immunosuppressed people or people without full polio vaccination. The candidate vaccines will be administered at the Centre for Evaluation of Vaccination - University of Antwerp and at the Center for Vaccinology, UGent and it is proposed that volunteers can leave the clinical setting after administration. The candidate vaccines will be administered orally, either as a single dose or as two consecutive doses with 28 days interval. Each dose contains approximately 10^6 $CCID_{50}$. Once administrated, the candidate vaccine virus can replicate and can be shed in nasopharyngeal secretions and faeces. A participant will be considered to have completed the study if he or she has completed all study related procedures 42 days after the last study vaccination and shedding is PCR negative on three consecutive stool samples (with a maximum of one sample per day).

Based on results of the first in human trial, for which the longest observed fecal shedding period comprised 89 days, it is anticipated that volunteers will shed the genetically modified Sabin OPV2 strains for several weeks. No nasopharyngeal shedding was observed in the first in human trial and data from literature reported fewer than 5% children shed virus from the oropharynx when challenge dose of OPV is administered to individuals who had previously received three or more doses of OPV. IPV and OPV both induce pharyngeal immunity and may both reduce oral-oral transmission.

Except for the measures proposed in the exclusion criteria aiming at reducing the exposure of vulnerable individuals or groups, the applicant is not proposing other 'containment' measures to limit dissemination into the environment which is in line with the applicants' claim that the risk on human health and the environment is considered negligible.

The questions raised by competent authorities of neighbouring countries, focused on i) how measures and/or exclusion criteria will be implemented or endorsed in view of minimizing the transboundary movement of volunteers and of the nOPV2 candidate vaccines and ii) the need to address more in depth the likelihood that the GM vaccine virus would spread to susceptible populations in other countries and the possible associated (delayed) effects. In its response the notifier further detailed possible scenarios potentially impacting unintentionally exposed individuals. Given the proposed conditions of release and measures to reduce the exposure of vulnerable individuals or groups, the Biosafety Advisory Council concludes that the environmental risk assessment can be extrapolated to receiving environments in neighbouring countries as no explicit distinction has to be made between vulnerable groups in Belgium or other neighbouring countries. Irrespective, the notifier proposes a set of additional measures that would further reduce exposure to vulnerable groups in neighbouring countries.

The Biosafety Advisory Council notes that, as with any other clinical trial with ambulatory volunteers, a transboundary movement of the product tested (in this case the GMO) cannot be excluded and further supports the view that, in terms of risk for the environment or human health, the proposed measures are proportionate and adequate in the context of the intended trial.

4. The risks for the environment or human health

Potential pathogenicity and mode of transmission for the nOPV2 candidate vaccines is expected to be no different than the vaccinal and parental OPV2. No health effects are anticipated for unintentionally exposed individuals, in particular when they have been effectively vaccinated. The mode of transmission, which is limited in case of effective vaccination, is primarily the result of person-to-person contact (fecal-oral or oral-oral).
With respect to the fecal-oral route and building on the estimation a 50% infectious dose for Sabin OPV2 correspond to 2.8 log $CCID_{50}$, exposure to a full infectious dose would require the ingestion of a significant amount of feces (for comparison, in the first in human study most positive samples after the peak shedding period had ca. 3 log $CCID_{50}$ of virus). Given the good sanitation and hygiene conditions (domestic and environmental hygiene standards, closed sewage systems) in Europe, the likelihood of occurrence of transmission through the fecal-oral route is low for close contacts of study participants and negligible for the population at large.
As mentioned, with respect to oral-oral route of transmission no nasopharyngeal shedding was observed in the first in human trial with the nOPV2 candidate vaccines and data from literature indicate IPV and OPV may both reduce oral-oral transmission.

Besides considerations on the likelihood of occurrence of secondary infection or inadvertent exposure, both the vaccination status of unintentionally infected individuals and the genetic stability of the nOPV2 candidate vaccines are key to the environmental risk assessment.

Due to the oral-oral transmission and oral-fecal transmission route and the persistence in the environment of these non-enveloped viruses, large groups of unvaccinated individuals may support

circulation of the nOPV2 candidate vaccines. This is because high vaccination coverage with OPV or IPV not only prevent disease from poliovirus but also hampers the circulation of poliovirus. It is expected that high immunization coverage with OPV or IPV will also hamper the circulation of nOPV2 candidate vaccines.

In regards the genetic stability of the two nOPV2 candidate vaccines it is likely that these will replicate in the human gut. Though the intended genetic modifications are aimed at obtaining genetically more stable viruses, the risk of potential genetic variants of the nOPV2 candidate vaccines was also assessed. As mentioned, primary results indicated an increased genetic and phenotypic stability of the nOPV2 candidates compared to Sabin OPV2. Therefore, the Biosafety Advisory Council supports the view that consequences of an unintentional transmission of a genetic variant of a nOPV2 candidate vaccine to an individual is likely be less hazardous than an unintentional transmission of genetic variants of the recipient Sabin OPV2 strain. Adverse effects associated to shedding and possible subsequent transmission of genetic variants of nOPV2 are negligible for immune-competent fully vaccinated individuals, low for unvaccinated immune-competent individuals and for people with immunodeficiency. Importantly, risks associated to person-to-person contact between selected study population and vulnerable people will be further mitigated by inclusion/exclusion criteria and clear instructions that will be provided to the participants and staff.

Though the generation of recombination events for both nOPV2 candidate vaccines is expected to be suppressed (candidate 1) or to result in variants that are more attenuated than Sabin OPV2 (candidate 2), the notifier was also asked to expand on the data that would support the conclusion that there is no evidence for circulation of type C enteroviruses in the Belgian population. Based on data of the National Reference Center for Enteroviruses, which receives 250 cerebrospinal fluid and stool samples per year (among which 100 samples every year are subject to enterovirus genotyping) and which has demonstrated the capacity to identify unknown recombinants using next generation sequencing, the Biosafety Advisory Council is of the opinion that the likelihood of recombination and hence the reversion of the attenuated candidate vaccine to a neurovirulent phenotype is negligible.

Finally, it can be noticed that in terms of risks to human health and the environment and taking into account the potential receiving environment of the intended trial, the potential consequences of releasing nOPV vaccine candidates or their genetic variants will at worst be comparable to the consequences associated to the historical use of Sabin OPV2 in routine vaccine campaigns in European countries (until 2001 in Belgium) and a Phase 4 study with OPV-vaccinated adults conducted in Belgium late 2015 (EudraCT 2015-003325-33). To our knowledge there have been no report of adverse consequences in terms of biosafety (risk for the environment or human population at large) associated to the use of Sabin OPV2 and its transmission in Belgium or its neighbouring countries over the last decades. Moreover, on the basis of the characteristics of the nOPV2 candidates and the proposed conditions of release (including proposed inclusion/exclusion criteria and instructions for study subjects), it can be reasonably assumed that risks, if any, are further mitigated to negligible.

5. The monitoring, control, waste treatment and emergency plans proposed by the applicant

The risks are primarily associated to potential genetic variants of nOPV2 candidate vaccines and are low for unvaccinated immune-competent individuals and people with immunodeficiency and negligible for immune-competent fully vaccinated individuals. Hence the Biosafety Advisory Council stresses the importance of the implementation and endorsement of the proposed inclusion/exclusion criteria and instructions for study subjects.
In its dossier the notifier submitted a detailed PCR protocol for the identification and detection of both nOPV vaccine candidates.

Conclusion

Based on the scientific assessment of the notification made by the Belgian experts, the Biosafety Advisory Council concludes that it is unlikely that the genetically modified OPV developed as live attenuated vaccine candidates will have any adverse effects on human health or on the environment in the context of the intended clinical trial and provided that all the foreseen safety measures are followed.

The Biosafety Advisory Council is of the opinion that elements presented both in the dossier and in the notifier's answers to the request of additional information are appropriate to conclude on the environmental risk assessment for the potential receiving environment taking into account the potential transboundary movement of the GMO to neighboring countries.

Therefore, the Biosafety Advisory Council issues a **positive advice with the following conditions**:

- The notifier and the investigators must strictly apply the clinical trial protocol, and all the exclusion/inclusion criteria and safety instructions as listed in Annex I.

- Any protocol amendment has to be previously approved by the Competent Authority.

- The notifier is responsible to verify that each study centre has qualified personnel experienced in handling infectious material and that the investigator has the required authorizations to perform the clinical trial activities inside the hospital (laboratory, pharmacy, hospital room, consultation room...) according to the Regional Decrees transposing Directive 2009/41/EC on contained use of genetically modified micro-organisms.

- The Biosafety Advisory Council should be informed within two weeks when the first patient starts the treatment and the last patient receives the last treatment.

- At the latest six months after the last visit of the last patient included in the trial, the notifier must send to the competent authority at the attention of the Biosafety Advisory Council a report with details concerning the biosafety aspects of the project. This report will at least contain:
    - The total number of patients included in the trial and the number of patients included in Belgium;
    - A summary of all adverse events marked by the investigators as probably or definitely related to the study medication;
    - A report on the consequences, if any, of the of deliberate release of nOPV2 candidate vaccines.

The Biosafety Advisory Council would like to point out that its conclusion relates to the risk for human health and the environment associated with the use of nOPV2 candidate vaccines and the potential emergence of genetic variants and is without prejudice to any management measure to be taken in the context of the WHO Polio Eradication Initiative to ensure and maintain high levels of vaccination coverage or to the WHO Global Action Plan to minimize poliovirus facility-associated risk after type-specific eradication of wild polioviruses and sequential cessation of oral polio vaccine use (GAP III).

Dr. Corinne Vander Wauven
President of the Belgian Biosafety Advisory Council

Annex I: List of exclusion/inclusion criteria and safety instructions
Annex II: Compilation of comments of experts in charge of evaluating the application B_BE_18_BVW2 (ref SC/1510/BAC/2018/0591)

Annex I: List of exclusion/inclusion criteria and safety instructions

List of inclusion and exclusion criteria in accordance with the clinical study protocol (UAM4).

At each visit participants will be reminded and checked for the inclusion and exclusion criteria and the necessity of adherence to the criteria will be reiterated.

Inclusion Criteria:

1. For OPV-vaccinated subjects to be allocated to groups 1, 2, 3 and 4: healthy males or females, from 18 to 50 years of age inclusive, having previously received at least 3 doses of OPV more than 12 months before the start of the study;
2. For IPV-only vaccinated subjects to be allocated to groups 5, 6 and 7: healthy males or females, from 15 to 50 years of age inclusive, having previously received at least 3 doses of IPV more than 12 months before the start of the study;
3. In good physical and mental health as determined on the basis of medical history and general physical examination performed at Day 0;
4. Female subjects of childbearing potential must agree to the use of an effective method of birth control throughout the study and up to 3 months after last vaccine dose (see Section 7);
5. Willing to adhere to the prohibitions and restrictions specified in this protocol (see Section 7);
6. Informed Consent Form (ICF) signed voluntarily by the subject and signed parental consent for adolescents before any study-related procedure is performed, indicating that the subject understands the purpose of any procedures required for the study and is willing to participate in the study.

Exclusion Criteria:

Subjects meeting any of the following criteria are excluded from participation in this study:

1. A condition that, in the opinion of the Investigator, could compromise the well-being of the subject or course of the study, or prevent the subject from meeting or performing any study requirements;
2. For Groups 5, 6 and 7: ever having received any OPV in the past;
3. Any travel to polio endemic countries or countries with evidence of recent (within last 6 months) wild or vaccine-derived poliovirus circulation during the total duration of the study;†
4. Professional handling of food, catering or food production activities during the total duration of the study;
5. Having Crohn's disease or ulcerative colitis or having had major surgery of the gastrointestinal tract involving significant loss or resection of the bowel;
6. A known allergy, hypersensitivity, or intolerance to the study vaccine or the placebo, or to any of their components or to any antibiotics;
7. Any confirmed or suspected immunosuppressive or immunodeficiency condition (including human immunodeficiency virus [HIV] infection, hepatitis B or C infections or total serum IgA level below laboratory lower limit of normal (LLN));
8. Will have household or professional contact with known immunosuppressed people or people without full polio vaccination (i.e. complete primary infant immunization series), e.g. babysitting during the total duration of the study;
9. Neonatal nurses or others having professional contact with children under 6 months of age during the total duration of the study;
10. Chronic administration (i.e., longer than 14 days) of immunosuppressant drugs or other immune-modifying drugs within 6 months prior to the first vaccine dose or planned use during the study. For instance, for corticosteroids, this means prednisone, or equivalent, ≥ 0.5 mg/kg/day (inhaled and topical

steroids are allowed whereas intra-articular and epidural injection/administration of steroids are not allowed);
11. Presence of contraindications to administration of the study vaccine on Day 0: acute severe febrile illness deemed by the Investigator to be a contraindication for vaccination or persistent diarrhea or vomiting;
12. Indications of drug abuse or excessive use of alcohol at Day 0 (males: > 21 units/week; females > 14 units/week);
13. Being pregnant or breastfeeding. Women of childbearing potential will undergo a urine pregnancy test at each vaccination visit. Subjects with a positive pregnancy test will be excluded;
14. Participation in another clinical study within 28 days prior to entry in this study or receipt of any investigational product (drug or vaccine) other than the study vaccine within 28 days prior to the first administration of study vaccine, or planned use during the study period;
15. Administration of any vaccine other than the study vaccine within 28 days prior to the first dose of study vaccine and during the entire study period;
16. Administration of any polio vaccine within 12 months before the start of the study;
17. Having had a transfusion of any blood product or application of immunoglobulins within the 4 weeks prior to the first administration of study vaccine or during the study;
18. Subject is an employee of the Investigator or study site, with direct involvement in the proposed study or other studies under the direction of that Investigator or study site, or is a family member of an employee or the Investigator, or was a study subject in the historical control studies UAM1 or UAT1 or in the study UAM4a;
19. Having a family or household member participating in the study CVIA 065 or being a study subject in the study CVIA 065.

List of additional safety instructions to ensure that exposure of the vulnerable groups is even more reduced:

Recruitment strategy

- For OPV-primed participants, recruitment of Belgian participants only.
- For the adult IPV-primed population, recruitment will occur in collaboration with the Dutch Embassy in Brussels to guarantee participation of Dutch volunteers living in Belgium. Targeted recruitment among members of Rotary clubs in Belgium will be envisaged because of their expected higher commitment and motivation to adhere to prohibitions and restrictions of the protocol.

Inclusion criteria of participants

- Weekly reminders via e-mail or sms will be sent to all study participants to emphasize the need and importance of hygienic measures as well as the importance of respecting the inclusion/exclusion criteria.
- Signature of the code of conduct at the start of the study

Instruction/information to participants

- Participants will be asked in addition to what is mentioned in the inclusion/exclusion criteria not to travel to the Netherlands, in particular to the Dutch Bible belt region, for a period of 3 months after administration of the first vaccine dose.
- Participants will be asked not to be in contact with relatives from regions known to have a lower prevalence of vaccination (e.g. the Dutch Bible belt)

Adviesraad voor Bioveiligheid
Conseil consultatif de Biosécurité

Compilation of comments of experts in charge of evaluating the dossier B/BE/18/BVW2

08 June 2018
Ref. SC/1510/BAC/2018_0591

Mandate for the Group of Experts: Mandate of the Biosafety Advisory Council (BAC) of 03 May 2018.
Coordinator: Karen Willard-Gallo (ULB)
Experts: Jean-Claude Twizere (ULg), Willy Zorzi (ULg)
SBB: Didier Breyer, Fanny Coppens, Katia Pauwels.

INTRODUCTION

Dossier **B/BE/18/BVW2** concerns a notification of the Centre for the Evaluation of Vaccination of University of Antwerp for deliberate release in the environment of genetically modified organisms other than higher plants according to Chapter II of the Royal Decree of 21 February 2005.
The notification has been officially acknowledged on 9 May 2018 and concerns a clinical trial with two novel live attenuated serotype 2 oral poliovirus vaccines (nOPV2) derived from the Sabin OPV2 that has been used for the eradication of type 2 polio. Through different combination of 5 distinct modified regions, the novel type 2 oral polio vaccine (nOPV2) candidates present modifications to the RNA sequences in the 5' untranslated region of polio genome (5' UTR), the capsid protein coding region (P1), the non-structural protein 2C, and the polymerase 3D of which only the latter result in a change in the amino acid sequence. It is hypothetized that the nOPV2 would more genetically stable and less prone for reversion to neurovirulent phenotype compared to Sabin OPV2 strain.
The application concerns a phase II multi-center study to evaluate the safety and immunogenicity of the two nOPV2 candidates, by oral administration to 332 health volunteers of which 200 have been vaccinated with OPV and 132 have been vaccinated with inactivated polio vaccine (IPV).

♦ INSTRUCTIONS FOR EVALUATION

Depending on their expertise, the experts were invited to evaluate the genetically modified organism considered in the notification as regards its molecular characteristics and its potential impact on human health and the environment. The pure medical aspects concerning the efficacy of the medicinal product and its safety for the treated patient are outside the scope of this evaluation.
The comments of the experts are roughly structured as in
- Annex II (principles for the risk assessment) of the Royal Decree of 21 February 2005
- Annex III (information required in notifications) of the Royal Decree of 21 February 2005
- Commission Decision 2002/623/EC of 24 July 2002 establishing guidance notes supplementing Annex II to Directive 2001/18/EC.

List of comments received from the experts

1. INFORMATION RELATED TO THE CHARACTERISTICS OF THE DONOR, THE RECIPIENT OR PARENTAL ORGANISM

(e.g. possibility of natural transfer of genetic material to other organisms, pathological, ecological and physiological characteristics, indigenous vectors ...)

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Has evaluated this item and has no questions/comments.

2. INFORMATION RELATED TO THE VECTOR

(e.g. description, sequence, mobilisation ...)

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Has evaluated this item and has no questions/comments.

3. INFORMATION RELATED TO THE CHARACTERISTICS OF THE GMO

3.1. Information related to the genetic modification

(e.g. methods used for the modification, description of the insert/vector construction ...)

Comment 1

Has evaluated this item and has no questions/comments but one typo error : Figure 3 : **re**presentation.

Comment 2

Has evaluated this item and has no questions/comments.

3.2. Information on the molecular characteristics of the final GMO

(e.g. number of copies of the transgenes, phenotypic and genetic stability of the transgenes, expression of the new genetic material, re-arrangements in the genome, inclusion or suppression of genetic material ...)

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Has evaluated this item and has no questions/comments.

3.3. Considerations for human, animal or plant health

(e.g. invasiveness and virulence, toxic or allergenic effects, possibility of survival outside of receiving host, other product hazards ...)

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Has evaluated this item and has no questions/comments.

4. INFORMATION RELATING TO THE CONDITION OF RELEASE

(e.g. description of the activity, quantities of GMO to be released, workers protection measures, elimination of any contaminating material in the preparation of the GMO stock, elimination of the GMO at the end of the experiment ...)

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Refers to his comment under section 6.2.

5. INFORMATION RELATED TO THE RISKS FOR THE ENVIRONMENT AND HUMAN HEALTH

5.1. Information on spread ("shedding") of the GMO from the treated patient/animal to other persons/animals or to the environment (including indirect/delayed effects due to vertical transmission to offspring).

(e.g. genetic transfer capability, routes of biological dispersal, target organisms ...)

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Has evaluated this item and has no questions/comments.

5.2. Information on possible effects on human health resulting from interactions of the GMO and persons working with, coming into contact with or in the vicinity of the GMO release (carekeepers, patient relatives, immunocompromised people ...).

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Refers to his comment under section 6.2.

5.3. Information on possible effects on animal health or on the environment.

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Has evaluated this item and has no questions/comments.

5.4. Information on selective advantages or disadvantages conferred to the GMO compared to the parental organism.

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Has evaluated this item and has no questions/comments.

5.5. Information on the possibility of the GMO to reconvert to his wild type form and possible consequences for human health or the environment.

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Has evaluated this item and has no questions/comments.

5.6. Information on the possibility of the GMO to exchange genetic material with other micro-organisms and possible consequences for human health or the environment.

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Has evaluated this item and has no questions/comments.

5.7. Information on the possibility of gene transfer to other organisms and about the selective advantages or disadvantages conferred to those resulting organisms (possible consequences for human health or the environment).

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Has evaluated this item and has no questions/comments.

6. INFORMATION RELATED TO THE MONITORING, SURVEILLANCE AND CONTROL, WASTE TREATMENT AND EMERGENCY PLANS PROPOSED BY THE APPLICANT

6.1. Monitoring plan proposed by the notifier and possibility to identify the occurrence of non-anticipated adverse effects.

(adequation between the monitoring plan and risks identified during the risk assessment, when appropriate measures to minimize the potential risks to offspring ...)

Comment 1

Has not evaluated this item.

Comment 2

Refers to his remark under section 6.2

6.2. Surveillance and control of the release

(adequation between the procedures to avoid and/or minimise the spread of the GMO and risks identified during the risk assessment...)

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

As indicated in point 5. of the SNIF draft 180426, all visits are ambulatory. After each of the several visits to the hospital to receive their treatment or to be monitored, the patients will go back home. At home, they will use their own toilet, bathroom, etc, in contact with other members of their family (children, pets), close people, people coming to their house…
In the SNIF dossier and in the ERA dossier, insufficient information is provided concerning the housekeeping care at home, especially concerning the decontamination of these rooms (SOP ? Provisioning of a disinfectant kit?…). There is also the question of the use of public toilets (open or restricted?) by the treated patients, eventually the indirect exposure of immuno-suppressed people using thereafter these facilities etc.

As indicated in points 7. , 9.b. and 10.b. of the SNIF dossier, the Polioviruses are resistant to inactivation by many common detergents and disinfectants, including soaps. Hence, these viruses may survive for a certain time in the environment (for weeks or even months in soil, for days in water).
But, taking into account firstly that the Polio immunization coverage for Belgium population estimated to be 98% (therefore there are no large groups of susceptible individuals that could support Polioviruses circulation) and secondly that the persistence of nOPV2 strains in the environment outside of a human host is limited, the consequences of the shedding by fecal way are considered by the notifier as severely limited (see point 2.1. of ERA dossier).
Therefore, the notifier proposed in:

- point I.2. of SNIF dossier:“ Post-release treatment of the GMOs. No treatment is envisaged of shed viruses. Participants will be asked to observe good hygienic practices. Material shed via feces will be discharged into the sewage system, in which it will be immediately diluted, and subsequent waste water treatment will substantially reduce virus concentrations.”)
- point I.3. of SNIF dossier:“No treatment is envisaged of shed viruses. Participants will be asked to observe hygienic practices such as flushing toilet with toilet lid closed, hand washing after toilet use…”).

Despite of this, the procedure to solve the problem of the fecal shedding, consisting in diluting the feces by usual flushing the toilet could be considered as being not sufficient to preserve the population against a potential exposure of nOPV2 strains. Considering that the treated patients have to return home during periods without clinical support and that the patients are having, at this time, direct or indirect contact with the population, there is a problem in the risk assessment.

SBB comment :

Taking into account the exclusion criteria during the total duration of the study (a.o. travelling to polio endemic countries or countries with evidence of recent (within last 6 months) wild or vaccine-derived poliovirus circulation; professional handling of food, catering or food production activities; having household or professional contact with known immunosuppressed people or people without full polio vaccination) and the good vaccination coverage in Belgium (mandatory routine vaccination with from 1966 up to 2001 use of the parental OPV vaccine from which the nOPV2 have been derived), it is confirmed that the applicant is proposing no further measures to limit dissemination into the environment which is in line with the applicants’ claim that the risk on human health and the environment is considered negligible.

6.3. Information on the waste generated by the activity and its treatment.
(e.g. type of waste, amount ...)

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Has evaluated this item and has no questions/comments.

6.4. If applicable, information on the emergency plan(s) proposed by the notifier.

Comment 1

Has not evaluated this item.

Comment 2

Has evaluated this item and has no questions/comments.

6.5 Information related to the identification of the GMO and the detection techniques
(e.g. identification methods and detection techniques, sensitivity, reliability and specificity of the proposed tests ..)

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Has evaluated this item and has no questions/comments.

7. OTHER INFORMATION

7.1 Do you have any other questions/comments concerning this notification that are not covered under the previous items?

Comment 1

This is an extremely well written and prepared study

Comment 2

None