Adviesraad voor Bioveiligheid
Conseil consultatif de Biosécurité

Advice of the Belgian Biosafety Advisory Council on the notification B/BE/19/BVW3 of the company Amgen for deliberate release in the environment of genetically modified organisms other than higher plants for research and development

13/05/2019
Ref. SC/1510/BAC/2019_0439

Context

The notification B/BE/19/BVW3 has been submitted by Amgen to the Belgian Competent Authority in February 2019 for a request of deliberate release in the environment of genetically modified organisms (GMO) 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 and the title of the notification is: **"A Phase 1, Multi-center, Open-label, Dose De-escalation Study to Evaluate the Safety and efficacy of Talimogene Laherparepvec in Pediatric Subjects With Advanced Noncentral Nervous System Tumors That are Amenable to Direct Injection"**. This multicentric clinical trial aims at investigating the safety and tolerability of the investigational medicinal product directly injected into the subject's tumours.

The investigational medicinal product, talimogene laherparepvec, is a recombinant herpes simplex type 1 virus (rHSV-1) attenuated by the functional deletion of two genes (ICP34.5 and ICP47) of the viral genome and genetically modified to express the human granulocyte macrophage colony-stimulating factor (hGM-CSF). The therapeutic strategy of talimogene laherparepvec is to allow replication of the recombinant virus within the tumour, to induce viral lysis of tumour cells and to induce an anti-tumour immune response enhanced by the local expression of hGM-CSF.

The parental organism, HSV-1, from which the disabled talimogene laherparepvec (rHSV-1) is derived, is an enveloped virus which is sensitive to and rapidly inactivated by both physical inactivation (dehydration, heat, low pH) and disinfectants (lipid solvents and mild detergents). It is also sensitive to acyclovir or any anti-viral drug that is activated by the viral thymidine kinase gene *in vivo*. It is a globally endemic pathogen of humans and has no known other natural host.

A total of ten patients are anticipated to be enrolled in the proposed clinical study in Europe. It can be expected that a maximum of two patients will be treated at the Belgian trial centre. The maximum daily dose is 4 ml x 10^6 PFU/ml (plaque forming unit(s)/millilitre). Subjects could receive 192 vials, over 24 months, which is approximately a total of 1.92 x 10^{10} PFU.

The trial centre is located in the Flemish region. The national territory is considered as the potential release area of the rHSV-1.

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On 16 December 2015, a marketing authorisation for Imlygic (EMEA/H/C/002771 – talimogene laherparepvec) has been issued with the indication of treatment of certain stages of melanoma by intralesional injections into injectable cutaneous, subcutaneous and nodal tumors[1]. Therefore, if the talimogene laherparepvec is used following the conditions of the marketing authorisation, no notification has to be submitted according to the Royal Decree of 21 February 2005.
The therapeutic strategy of the current clinical trial involves intralesional injections into noncentral nervous system tumors in pediatric subjects. The changed indication compared to the market authorised indication justifies an evaluation of elements for the environmental risk assessment in the context of the current dossier. Since the characteristics of the GMO had already been assessed by the BAC in the framework of five previous notifications (B/BE/14/BVW1, B/BE/15/BVW1, B/BE/15/BVW2, B/BE/16/BVW1 and B/BE/17/BVW2)[2], the competent authority agreed to ask the applicant to focus its assessment on aspects related to the potential environmental impact of the physical condition of the pediatric subjects with noncentral nervous system tumors.

The dossier has been officially acknowledged by the Competent Authority on 19 March 2019 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 one expert to evaluate the dossier. The expert assessed whether the information provided in the notification was sufficient and accurate in order to state that the deliberate release of the GMO 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) in the context of the intended use and concluded there were no further remarks.

The analytical procedure for the detection of rHSV-1 had already been submitted in the framework of notification B/BE/14/BVW1 and evaluated at that time by the Platform Biotechnology and Molecular Biology of the Scientific Institute of Public Health (currently Sciensano).

The scientific evaluation has been performed considering the 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 Investigational Medicinal Product (IMP) and its safety for the treated patient, 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 one comment from the public, not dealing with biosafety.

[1] https://www.ema.europa.eu/en/medicines/human/EPAR/imlygic
[2] Advice on the notification B/BE/17/BVW2 of 27/09/2017 (ref BAC_2017_0748) and its annexes

Summary of the scientific evaluation

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

See advice of the BAC on the notification B/BE/17/BVW2 (Annex 2 and annexes therein).

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

See advice of the BAC on the notification B/BE/17/BVW2 (Annex 2 and annexes therein).

3. The conditions of the release

Special instructions for the handling and use of the GMO are provided in the Investigator Brochure. To avoid direct contact with skin, eyes and mucous membranes, the BAC recommends that personnel manipulating the GMO are instructed to wear a laboratory coat, closed shoes, gloves, mouth mask and safety glasses. Internal transport of the vials containing the GMO should be performed in a hermetic transport box containing absorbent paper towels.
Since no additional information about the containment measures and instructions for use were provided in the current notification as compared to the previous notifications, the BAC recommends that the same measures and instructions than those described for the previous clinical trials involving Imlygic are followed. This is for the most part described in p.60 in the Investigator Brochure. In particular, the BAC refers to the Investigational Product Instruction Manual (IPIM) and the Healthcare information sheet notification provided in the framework of notification B/BE/16/BVW1 with respect to the measures to prevent inadvertent release of the GMO and the instructions prepared for the personnel, respectively.

4. The risks for the environment or human health

Talimogene laherparepvec will be administered by intralesional injection only into injectable cutaneous, subcutaneous, nodal tumors, and other non-visceral tumors. The first dose of talimogene laherparepvec will be up to 4.0 ml of 10^6 PFU/ml, followed by subsequent injections at defined intervals (up to 4.0 ml of 10^8 PFU/ml, or up to 4.0 ml of 10^6 PFU/ml for a dose de-escalated cohort). The mode of administration and the injection doses are similar to those already assessed in the framework of previous clinical trial notifications and in the authorised indication. The BAC is of the opinion that changes in probability of shedding in blood and urine compared to previous trials conducted in Belgium cannot be excluded. However, this will not increase the risks for the environment or the human health provided that all safety measures described in the dossier are followed.
The BAC also agrees with the notifier that it is unlikely that the level of risk associated with talimogene laherparepvec in pediatric subjects with advanced solid tumors will be different to that experienced by the adult population.
Patients and close contacts are advised to avoid touching or scratching injection sites as this could lead to inadvertent transfer of talimogene laherparepvec. Close contacts who are pregnant or immunocompromised should not change the subject's dressings or clean their injection sites.

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

As in the previous clinical trial notifications, the monitoring activities foreseen for this clinical trial cover swabbing of any lesions suspected to be of herpetic origin in patients, patients' close contacts, health

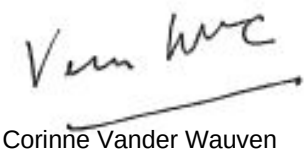
care providers and caregivers for testing of talimogene laherparepvec DNA. Waste materials will be disposed of in line with standard practice for medical waste. Subjects should place used dressings and cleaning materials in a sealed plastic bag and dispose in household waste or return to the study site depending on local guidance.

Conclusion

Based on the scientific assessment of this dossier made by the Belgian expert, taking into account the previous advices on notifications B/BE/14/BVW1, B/BE/15/BVW1, B/BE/15/BVW2, B/BE/16/BVW1 and B/BE/17/BVW2, and considering the data presently available, the Biosafety Advisory Council concludes that it is unlikely that talimogene laherparepvec developed for oncolytic immunotherapy will have any adverse effects on human health or the environment in the context of the intended clinical trial and provided that all the foreseen safety measures are followed.

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 as described in the current dossier and all the safety instructions as described in the current dossier and in the notification B/BE/16/BVW1.
- 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 authorisations 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 the contained use of genetically modified micro-organisms.
- The BAC 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 the competent authority for the attention of the BAC a report with details concerning the biosafety aspects of the project. This report shall contain at least:
  - 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 accidental releases, if any, of the recombinant HSV-1.



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

Annex I: *Compilation of comments of the expert in charge of evaluating the dossier B/BE/19/BVW9 (ref. SC/1510/BAC/2019_0374)*
Annex II: *Advice of the Belgian Biosafety Advisory Council on the notification B/BE/17/BVW2 of the company Amgen for deliberate release in the environment of genetically modified herpes simplex type 1 virus (HSV-1) for research and development (ref. WIV-ISP/41/BAC/2017_0748). This advice contains in annex all the advices related to clinical trials in Belgium involving talimogene laherparepvec.*

Compilation of comments of experts in charge of evaluating the dossier B/BE/19/BVW3

27 March 2019
Ref. SC/1510/BAC/2019_0374

Mandate for the Group of Experts: Mandate of the Biosafety Advisory Council (BAC) of 19 March 2019.
Coordinator: Jozef Anné (KUL)
Expert: SBB, Sciensano
SBB: Didier Breyer

INTRODUCTION

Dossier **B/BE/19/BVW3** concerns a notification from Amgen Ltd for the 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 19 March 2019. It concerns a clinical trial entitled "*A Phase 1, Multi-center, Open-label, Dose De-escalation Study to Evaluate the Safety and Efficacy of Talimogene Laherparepvec in Pediatric Subjects with Advanced Non Central Nervous SystemTumors That are Amenable to Direct Injection*".

♦ INSTRUCTIONS FOR EVALUATION

This dossier involves a product (Talimogene laherparepvec, a recombinant herpes simplex virus 1) that has already been evaluated by the Biosafety Advisory Council in the framework of previous clinical trials (B/BE/14/BVW1, B/BE/15/BVW1, B/BE/15/BVW2, B/BE/16/BVW1 and B/BE/17/BVW2).
The product is already approved for commercialization in the European market under the name Imlygic. Because this new clinical trial has a changed indication compared to the market authorised indication (new treatment involving pediatric subjects), a new request for authorization under Chapter II of the Royal Decree of 21 February 2005 was necessary. However, the competent authority agreed to ask the applicant to provide a simplified environmental risk assessment focusing on aspects that are specific to this new deliberate release.

The expert was invited to evaluate whether the new information provided in the notification was sufficient and accurate in order to state that the deliberate release of the GMO 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) in the context of the intended use. 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 expert 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.

Comments/questions received from the expert

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

This part has been evaluated in a previous dossier (B/BE/14/BVW1).

***Comment SBB**:*
This item has already been thoroughly assessed by the Biosafety Council in the frame of the previous dossiers involving the same GMO.

2. INFORMATION RELATED TO THE VECTOR

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

Comment

This part has been evaluated in a previous dossier (B/BE/14/BVW1).

***Comment SBB**:*
This item has already been thoroughly assessed by the Biosafety Council in the frame of the previous dossiers involving the same GMO.

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

This part has been evaluated in a previous dossier (B/BE/14/BVW1).

***Comment SBB**:*
This item has already been thoroughly assessed by the Biosafety Council in the frame of the previous dossiers involving the same GMO.

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

This part has been evaluated in a previous dossier (B/BE/14/BVW1).

***Comment SBB**:*
This item has already been thoroughly assessed by the Biosafety Council in the frame of the previous dossiers involving the same GMO.

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

This part has been evaluated in a previous dossier (B/BE/14/BVW1).

***Comment SBB**:*
This item has already been thoroughly assessed by the Biosafety Council in the frame of the previous dossiers involving the same GMO.

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

The applicant does not describe the containment measures used for the injection of the GMO to the children (worker's protection measures, waste management…). How long stay the children in the hospital?
In the previous dossier, the applicant describes the following instructions: "disposal of any soiled dressings should occur via the study site at their next scheduled visit. The subject is provided with additional dressings, disposable gloves and resealable bags, and specific instructions to be followed to minimise the risk of unintended exposure to the environment."
Are these instructions the same as described in the previous dossier?

***Comment SBB**:*
In the SNIF (section I.3.b) it is stated that:"Since talimogene laherparepvec will be administered in a medical facility, all associated waste will be disposed of in line with standard practice for medical waste. The information leaflet provided to each subject instructs that disposal of any soiled dressings should

occur via the study site at their next scheduled visit. The subject is provided with additional dressings, disposable gloves and resealable bags, and specific instructions to be followed to minimise the risk of unintended exposure to the environment."
Special instructions for use and handling is provided in the Investigator Brochure (page 60).
Since the notifier does not provide additional information about the containment measures and instructions for use, it can be anticipated that these are the same as for the previous clinical trials with Imlygic.

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

The shedding of the GMO in the urine cannot be excluded. The applicant should describe how the diapers are eliminated at the hospital and at home.

***Comment SBB**:*
Instructions are provided on pages 60-61 of the Investigator Brochure:
"Advise subjects to place used dressings and cleaning materials in a sealed plastic bag and dispose in household waste or return to the study site depending on local guidance."

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

The treated patients should avoid any contact with immunocompromised persons. This is not described in the dossier.

***Comment SBB**:*
Special warnings are described on page 62 of Investigator Brochure:
"Subjects should be advised to avoid touching or scratching injection sites as this could lead to inadvertent transfer of talimogene laherparepvec to other areas of their body. Close contacts who are pregnant or immunocompromised should not change the subject's dressings or clean their injection sites."

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

Comment

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

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

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

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

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

Has evaluated this item and has no questions/comments.

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

The applicant does not describe in the dossier the containment measures and work practices used for the injection of the GMO to children. Are these measures the same as those describe in the previous dossier?

***Comment SBB**:*
See comment SBB under item 4.

6.3. Information on the waste generated by the activity and its treatment.

(e.g. type of waste, amount ...)

Comment

The applicant does not describe in the dossier the waste management. The applicant should described how the material contaminated with the GMO and the diapers are eliminate at the hospital and at home.

***Comment SBB**:*
Instructions are provided on pages 60-61 of the Investigator Brochure:
"- Dispose of all materials that have come in contact with talimogene laherparepvec (e.g., vial, syringe, needle, any cotton or gauze) in accordance with local institutional procedures.
- Advise subjects to place used dressings and cleaning materials in a sealed plastic bag and dispose in household waste or return to the study site depending on local guidance."

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

Comment

Has not evaluated this item

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

Has not evaluated this item

7. OTHER INFORMATION

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

Comment

None

References

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Bioveiligheidsraad
Conseil de Biosécurité

27-09-2017

Secretariaat
Secrétariat

O./ref.: WIV-ISP/41/BAC/2017_0748

Advice of the Belgian Biosafety Advisory Council on the notification B/BE/17/BVW2 of the company Amgen for deliberate release in the environment of genetically modified herpes simplex type 1 virus (HSV-1) for research and development

Context

The notification B/BE/17/BVW2 has been submitted by Amgen to the Belgian Competent Authority in August 2017 for a request of deliberate release in the environment of genetically modified organisms (GMO) 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 and the title of the notification is: **"A Phase 1b Study of Talimogene Laherparepvec in Combination With Atezolizumab in Subjects With Triple Negative Breast Cancer and Colorectal Cancer With Liver Metastases"**. This multicentric clinical trial aims at investigating the safety of intrahepatic injection of the investigational medicinal product (Talimogene Laherparepvec) into liver metastases in combination with intravenously administered monoclonal antibody (atezolizumab) administered separately in subjects with triple-negative negative breast cancer (cohort 1) and colorectal cancer (cohort 2).

The investigational medicinal product, Talimogene laherparepvec, is a recombinant herpes simplex type 1 virus (rHSV-1) attenuated by the functional deletion of two genes (ICP34.5 and ICP47) of the viral genome and genetically modified to express the human granulocyte macrophage colony-stimulating factor (hGM-CSF). The therapeutic strategy of Talimogene laherparepvec is to allow replication of the recombinant virus within the tumour, to induce viral lysis of tumour cells and to induce an anti-tumour immune response enhanced by the local expression of hGM-CSF.

After the initial dose, subsequent doses of Talimogene laherparepvec will be given every 21 days thereafter and up to 6 doses may be administered. After 6 initial intrahepatic cycles, there is an option to continue treatment with an additional 6 cycles by means of intralesional injections into liver metastases or cutaneous, subcutaneous or nodal tumor lesions. If possible, the protocol foresees to administer atezolizumab prior to talimogene laherparepvec. If either atezolizumab or talimogene laherparpevec administration is delayed due to toxicity,

the protocol foresees to delay the cycle until both investigational products can be administered safely in combination.
The parental organism, HSV-1, from which the disabled talimogene laherparepvec (rHSV-1) is derived, is an enveloped virus which is sensitive to and rapidly inactivated by both physical inactivation (dehydration, heat, low pH) and disinfectants (lipid solvents and mild detergents). It is also sensitive to acyclovir or any anti-viral drug that is activated by the viral thymidine kinase gene *in vivo*. It is a globally endemic pathogen of humans and has no known other natural host.
The trial centres are located in Brussels and in Flanders. The national territory is considered as the potential release area of the rHSV-1.

On 16 December 2015, a marketing authorisation for Imlygic (EMEA/H/C/002771 – talimogene laherparepvec) has been issued with the indication of treatment of certain stages of melanoma by intralesional injections into injectable cutaneous, subcutaneous and nodal tumors[1]. As a consequence, if the talimogene laherparepvec is used following the conditions of the marketing authorisation, no notification has to be submitted according to the Royal Decree of 21 February 2005.
The therapeutic strategy of the current clinical trial aims an initial intrahepatic injection into liver tumors, expanded by cycles of intralesional injections into liver metastases or cutaneous, subcutaneous or nodal tumor lesions if judged necessary. The initial intrahepatic injection into liver tumors together with a changed indication compared to the market authorised indication justifies an evaluation of elements for the environmental risk assessment in the context of the current dossier. Since the characteristics of the GMO had already been assessed by the BAC in the framework of four previous notifications (B/BE/14/BVW1, B/BE/15/BVW1, B/BE/15/BVW2 and B/BE/16/BVW1)[2], the competent authority agreed to ask the applicant to focus its assessment on aspects related to the potential impact of the combined therapy of Talimogene Laherparepvec and Atezolizumab and the potential impact of the physical condition of the subjects with Triple Negative Breast and Colorectal Cancer With Liver Metastases.

The dossier has been officially acknowledged by the Competent Authority on 4 August 2017 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 one expert to evaluate the dossier. The expert assessed whether the information provided in the notification was sufficient and accurate in order to state that the deliberate release of the GMO 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) in the context of the intended use and concluded there were no further remarks.

The analytical procedure for the detection of rHSV-1 had already been submitted in the framework of notification B/BE/14/BVW1 and evaluated at that time by the Platform Biotechnology and Molecular Biology of the Scientific Institute of Public Health.

[1] http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002771/smops/Positive/human_smop_000894.jsp&mid=WC0b01ac058001d127
[2] Advice on the notification B/BE/16/BVW1 of 13 December 2016 (ref BAC_2016_0790) and its annexes – see Annex 1

The scientific evaluation has been performed considering the 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 Investigational Medicinal Product (IMP) and its safety for the treated patient, 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 three comments from the public of which one is dealing with biosafety. The comment has been considered by the BAC in the preparation of the current advice (Annex 1).

Summary of the scientific evaluation

1. Characteristics of the donor, recipient or parental organism

See advice of the BAC on the notification B/BE/14/BVW1 (Annex 2 and annexes therein).

2. Characteristics of the GMO and of the medication

See advice of the BAC on the notification B/BE/14/BVW1 (Annex 2 and annexes therein).

3. Conditions of release

The applicant refers to the Investigational Product Instruction Manual (IPIM) and the Healthcare information sheet notification provided in the framework of notification B/BE/16/BVW1 with respect to the measures to prevent inadvertent release of the GMO and the instructions prepared for the personnel. To avoid direct contact with skin, eyes and mucous membranes, personnel manipulating the GMO are instructed to wear a laboratory coat, closed shoes, gloves, mouth mask and safety glasses. Internal transport of the vials containing the GMO should be performed in a hermetic transport box containing absorbent paper towels.

4. Potential risks for the environment, animal or human health associated with the release of the GMO

Subjects will receive six initial intrahepatic cycles of Talimogene laherparepvec, a mode of administration that has already been assessed in the context of notification B/BE/16/BVW1. Treatment of the subjects can be continued by means of additional cycles of intralesional injections into cutaneous, subcutaneous or nodal tumor lesions, a mode of administration that has already been assessed in the framework of notification B/BE/14/BVW1, B/BE/15/BVW1 and B/BE/15/BVW2. The BAC is of the opinion that changes in probability of shedding in

blood and urine compared to previous trials conducted in Belgium cannot be excluded but that this will not increase the risks for the environment nor the human health provided that all safety measures described in the dossier are followed.
By referring further to notification B/BE/16/BVW1, the applicant provided instructions for patient's close contacts or family members who are pregnant or have a weakened immune system.
The current dossier is further characterized by a combined therapy of Talimogene Laherparepvec with Atezolizumab, which is a humanised monoclonal antibody that binds to PD-L1 and blocks its interactions with both PD-1 and B7.1 receptors. The Biosafety Advisory Council notes that that there are no evidences pointing to a direct impact of the monoclonal anti-PD-1 antibody on the ability of replication of Talimogene laherparepvec.

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

As in the previous notifications, the monitoring activities foreseen for this clinical trial cover swabbing of any lesions suspected to be of herpetic origin in patients, patients' close contacts, health care providers and caregivers for testing of Talimogene laherparepvec DNA. Waste materials will be incinerated after decontamination.

Conclusion

Based on the scientific assessment of this dossier made by the Belgian expert, taking into account the previous advices on notifications B/BE/14/BVW1, B/BE/15/BVW1, B/BE/15/BVW2 and B/BE/16/BVW1 and considering the data presently available, the Biosafety Advisory Council concludes that it is unlikely that Talimogene laherparepvec developed for oncolytic immunotherapy will have any adverse effects on human health or the environment in the context of the intended clinical trial and provided that all the foreseen safety measures are followed.
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 as described in the current dossier and all the safety instructions as described in the notification B/BE/16/BVW1 (see Annex 2).
- 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 authorisations 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 the contained use of genetically modified micro-organisms.
- For the transport of the IMP the notifier should conform to the transportation rules regarding transport of GMOs.
- The BAC 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 the competent authority for the attention of the BAC a report with details concerning the biosafety aspects of the project. This report shall contain at least:
  - 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 accidental releases, if any, of the recombinant HSV-1.

Prof. M. De Proft
President of the Belgian Biosafety Advisory Council

Annex 1: Answer of the Belgian Biosafety Advisory Council to the comment made during the public consultation on the notification B/BE/17/BVW2 (ref. BAC_2017_0753)
Annex 2 : Advice on the notification B/BE/16/BVW1 of 13 December 2016 (ref. BAC_2016_0790) and its annexes

Bioveiligheidsraad
Conseil de Biosécurité

27-09-2017

Secretariaat
Secrétariat

O./ref.: WIV-ISP/41/BAC_2017_0753

Answer of the Belgian Biosafety Advisory Council to the comment made during the public the public consultation on the notification B/BE/17/BVW2 of the company Amgen for deliberate release in the environment of genetically modified organisms other than higher plants for research and development

Context

The notification B/BE/17/BVW2 has been submitted by Amgen to the Belgian Competent Authority in August 2017 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 notification has been officially acknowledged by the Competent Authority (CA) on 4 August 2017.

According to article 17 of the Royal Decree, the CA organised a one-month public consultation. As a result of this consultation, the CA forwarded to the Biosafety Advisory Council the comment from the public, of which one single comment related to biosafety.

According to article 16§2 of the Royal Decree, this comment has been taken into account in the elaboration of the advice of the Biosafety Advisory Council (ref. BAC_2017_0748). Answer to this comment is given below.

Public questions/comments raising non-biosafety issues (such as economical or ethical issues) are not considered by the Biosafety Advisory Council.

Comment from the public considered by the Biosafety Advisory Council

The public consultation resulted in one query about what inactivating agents will be used in case of accidental spill and whether the inactivating agents will be made available for the patients and their close contacts.

Answer

Actions to take in case of accidental exposure to Talimogene Laherparepvec and waste management procedures are unchanged compared to those that have been described in the context of the previous dossiers (e.g. B/BE/16/BVW1 - healthcare information sheet). After administration of talimogene laherparepvec, the injection site will be covered with an

occlusive dressing (a dressing that is water tight) that must be kept in place for up to 1 week. Patients will be given extra dressings to take home and a sealable bag. If the dressings need to be changed while at home, patients must put the used dressing in the provided bag and seal properly. This must be given to a research team member for waste disposal.

Any potential or known unintended exposure should be reported to Amgen within 24 hours of the investigator's knowledge of the event of exposure. Amgen will seek to follow-up with the exposed individual, if necessary, to collect more information about the exposed individual contact with clinical trial subject, signs and/or symptoms related to the exposure, medical history, and/or outcome of the exposure. If the exposed individual is reporting signs or symptoms suspected to be related to talimogene laherparepvec exposure, the exposed individual may be asked to have a swab taken to evaluate for the presence of talimogene laherparepvec DNA in the lesion.

The parental organism, Herpes simplex 1 virus (HSV-1) and its disabled derivative talimogene laherparepvec are enveloped viruses which are sensitive to and rapidly inactivated by both physical inactivation (dehydration, heat, low pH) and disinfectants (lipid solvents, mild detergents and bleach 2.5% v/v, the latter which can be widely obtained). They are also sensitive to acyclovir or any anti-viral drug that is activated by the viral thymidine kinase gene and may be administered, if clinically indicated. Moreover, as a preventive measure, close contacts that are pregnant or have a weakened immune system should not change the patient's dressing or clean the injection site.

Bioveiligheidsraad
Conseil de Biosécurité

13-12-2016

Secretariaat
Secrétariat

O./ref.: WIV-ISP/41/BAC/2016_0790

Title: Advice of the Belgian Biosafety Advisory Council on the notification B/BE/16/BVW1 of the company Amgen for deliberate release in the environment of genetically modified herpes simplex type 1 virus (HSV-1) for research and development

Context

The notification B/BE/16/BVW1 has been submitted by Amgen to the Belgian Competent Authority in October 2016 for a request of deliberate release in the environment of genetically modified organisms (GMO) 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 and the title of the notification is: **"A Phase 1, Multicenter, Open-label Trial to Evaluate the Safety of Talimogene Laherparepvec Injected into Liver Tumors"**. The clinical trial aims at investigating the safety of the investigational medicinal product when injected into hepatocellular carcinoma and metastatic liver tumors.

The investigational medicinal product, Talimogene laherparepvec, is a recombinant herpes simplex type 1 virus (rHSV-1) attenuated by the functional deletion of two genes (ICP34.5 and ICP47) of the viral genome and genetically modified to express the human granulocyte macrophage colony-stimulating factor (hGM-CSF). The therapeutic strategy of Talimogene laherparepvec is to allow replication of the recombinant virus within the tumour, to induce viral lysis of tumour cells and to induce an anti-tumour immune response enhanced by the local expression of hGM-CSF.

Talimogene laherparepvec is administered by intrahepatic injection into liver tumours. After the initial dose, subsequent doses will be given every 21 days thereafter and up to 6 doses may be administered. The parental organism, HSV-1, is an enveloped virus which is sensitive to and rapidly inactivated by both physical inactivation (dehydration, heat, low pH) and disinfectants (lipid solvents and mild detergents). It is a globally endemic pathogen of humans and has no known other natural host.
The trial centres are located in Brussels and in Flanders. The national territory is considered as the potential release area of the rHSV-1.

The dossier has been officially acknowledged by the Competent Authority on 3 November 2016 and forwarded to the Biosafety Advisory Council (BAC) for advice.

On 16 December 2015, a marketing authorisation for Imlygic (EMEA/H/C/002771 – talimogene laherparepvec) has been issued with the indication of treatment of certain stages of melanoma by intralesional injections into injectable cutaneous, subcutaneous and nodal tumors[1]. As a consequence, if the talimogene laherparepvec is used following the conditions of the marketing authorisation, no notification has to be submitted according to the Royal Decree of 21 February 2005.
The therapeutic strategy of the current clinical trial aims an intrahepatic injection into liver tumors, thereby justifying an evaluation of elements for the environmental risk assessment in the context of the current dossier.
Within the framework of the evaluation procedure, the BAC, under the supervision of a coordinator and with the assistance of its Secretariat, contacted one expert to evaluate the dossier, taking into account that Talimogene laherparepvec had already been assessed by the BAC in the framework of three previous notifications (B/BE/14/BVW1, B/BE/15/BVW1 and B/BE/15/BVW2)[2,3,4].
The expert assessed whether the information provided in the notification was sufficient and accurate in order to state that the deliberate release of the GMO 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) in the context of the intended use. Since the characteristics of the GMO had already been assessed previously, the assessment of the current notification focused on the specific conditions of the release taking into account the change of indication. See Annex 1 for an overview of the comments of the expert.

The analytical procedure for the detection of rHSV-1 had already been submitted in the framework of notification B/BE/14/BVW1 and evaluated at that time by the Platform Biotechnology and Molecular Biology of the Scientific Institute of Public Health.

The scientific evaluation has been performed considering the 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 Investigational Medicinal Product (IMP) and its safety for the treated patient, 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 one comment from the public partly dealing with biosafety, which has been considered by the BAC in the preparation of the current advice.

[1] http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002771/smops/Positive/human_smop_000894.jsp&mid=WC0b01ac058001d127
[2] Advice on the notification B/BE/14/BVW1 of 24 February 2015 (ref BAC_2015_0113) – see Annex 2
[3] Advice on the notification B/BE/15/BVW1 of 12 October 2015 (ref BAC_2015_0679) – see Annex 3
[4] Advice on the notification B/BE/15/BVW2 of 12 January 2016 (ref BAC_2016_0023) – see Annex 4

Summary of the scientific evaluation

1. Characteristics of the donor, recipient or parental organism

See advice of the BAC on the notification B/BE/14/BVW1 (Annex 2).

2. Characteristics of the GMO and of the medication

See advice of the BAC on the notification B/BE/14/BVW1 (Annex 2).

3. Conditions of release

In the framework of the evaluation of the notification B/BE/14/BVW1 the BAC had several criticisms relating to the measures to prevent inadvertent release of the GMO and the instructions prepared for the personnel. It was advised to instruct personnel manipulating the GMO to wear a mask and closed shoes, and to perform the internal transport of the vials containing the GMO in a hermetic transport box containing absorbent paper towels.
These remarks were taken into account by the notifier in this new dossier by providing a country-specific addendum to the Investigational Product Instruction Manual (IPIM) and by adapting the Healthcare information sheet accordingly.

4. Potential risks for the environment, animal or human health associated with the release of the GMO

The current dossier is characterized by intrahepatic injection of Talimogene laherparepvec, into injectable liver lesions of patients with hepatocellular carcinoma. In the context of the evaluation of previous dossiers involving intralesional injection of Talimogene laherparepvec into cutaneous, subcutaneous and nodal tumours the probability of shedding via blood and urine has been taken into account. Compared to these previous notifications, the BAC is of the opinion that the intrahepatic injection may be associated in changes in probability of shedding in blood and urine but that this will not increase the risks for the environment nor the human health provided that all safety measures described in the dossier are followed.
It was further noted that the notifier took into account the remarks of the BAC addressed in the context of the notification B/BE/14/BVW1, thereby providing clear instructions for patient's close contacts or family members who are pregnant or have a weakened immune system.

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

As in the previous notification (B/BE/15/BVW1), the monitoring activities foreseen for this clinical trial cover swabbing of any lesions suspected to be of herpetic origin in patients, patients' close contacts, health care providers and caregivers for testing of Talimogene laherparepvec DNA. Waste materials will be incinerated after decontamination.

Conclusion

Based on the scientific assessment of this dossier made by the Belgian expert, taking into account the previous advices on notifications B/BE/14/BVW1, B/BE/15/BVW1 and B/BE/15/BVW2 and considering the data presently available, the Biosafety Advisory Council concludes that it is unlikely that Talimogene laherparepvec developed for oncolytic immunotherapy will have any adverse effects on human health or the environment in the context of the intended clinical trial and provided that all the foreseen safety measures are followed.

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 safety instructions as described in the dossier.
- 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 authorisations 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 the contained use of genetically modified micro-organisms.
- For the transport of the IMP the notifier should conform to the transportation rules regarding transport of GMOs.
- The BAC 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 the competent authority for the attention of the BAC a report with details concerning the biosafety aspects of the project. This report shall contain at least:
  - 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 accidental releases, if any, of the recombinant HSV-1.

Prof. M. De Proft
President of the Belgian Biosafety Advisory Council

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Annex 1: Compilation of comments of the experts in charge of assessing the notification B/BE/16/BVW1 (ref: BAC_2016_0769)

Annex 2: Advice of the Belgian Biosafety Advisory Council on the notification B/BE/14/BVW1 of the company Amgen for deliberate release in the environment of genetically modified organisms other than higher plants for research and development (ref. BAC_2015_0113)

Annex 3: Advice of the Belgian Biosafety Advisory Council on the notification B/BE/15/BVW1 of the company Amgen for deliberate release in the environment of genetically modified organisms other than higher plants for research and development (ref. BAC_2015_0679)

Annex 4: Advice of the Belgian Biosafety Advisory Council on the notification B/BE/15/BVW2 of the company Amgen for deliberate release in the environment of genetically modified organisms other than higher plants for research and development (ref. BAC_2016_0023)

Bioveiligheidsraad
Conseil de Biosécurité

05 December 2016

Secretariaat
Secrétariat

O./ref.: WIV-ISP/41/BAC_2016_0769
Email: bac@wiv-isp.be

Compilation of comments of experts in charge of assessing the dossier B/BE/16/BVW1

Mandate for the Group of Experts: Mandate of the Biosafety Advisory Council (BAC) of 3 November 2016
Coordinator: Prof. Jozef Anné (KUL)
Experts: Aline Baldo (WIV-ISP, SBB)
Domains of expertise of experts involved: Molecular genetics, virology, biosafety, contained use
Secretariat (SBB): Didier Breyer, Fanny Coppens, Katia Pauwels

INTRODUCTION

Dossier **B/BE/16/BVW1** concerns a notification of the company Amgen Ltd 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 3 November 2016 and concerns a clinical trial with Talimogene laherparepvec a recombinant Herpes simplex virus 1. The herpes virus has been attenuated by the functional deletion of two genes (ICP34.5 and ICP47) of the HSV-1 genome and has been genetically modified to express granulocyte-macrophage colony-stimulating factor (GM-CSF). The intended therapeutic strategy is to produce a direct oncolytic effect by replication of the virus within the tumour, and induction of an anti-tumour immune response, enhanced by the local expression of hGM CSF. The clinical trial aims at intrahepatic injection of Talimogene laherparepvec into liver tumors. After the initial dose, subsequent doses will be given every 21 days thereafter and up to 6 doses may be administered.

On 16 December 2015, a marketing authorisation for Imlygic (EMEA/H/C/002771–talimogene laherparepvec) has been issued with the indication of treatment of certain stages of melanoma by intralesional injections into injectable cutaneous, subcutaneous and nodal tumors[1]. As a consequence, if the talimogene laherparepvec is used following the conditions of the marketing authorisation, no notification has to be submitted according to the Royal Decree of 21 February 2005.
The therapeutic strategy of the current clinical trial aims an intrahepatic injection into liver tumors, thereby justifying an evaluation of elements for the environmental risk assessment in the context of the current dossier.

[1] http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002771/smops/Positive/human_smop_000894.jsp&mid=WC0b01ac058001d127

Talimogene laherparepvec was already notified by Amgen in August 2014 in dossier B/BE/14/BVW1 (for subjects with *untreated, unresected stage IIIB to IVM1c melanoma)*, dossier B/BE/15/BVW1 (combined with pembrolizumab for subjects with *untreated, unresected stage IIIB to IVM1c melanoma*) and dossier B/BE/15/BVW2 (combined with pembrolizumab for treatment of subjects with *recurrent metastatic squamous cell carcinoma of the head and neck*).

- **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

Remark: Based on the comments and remarks below, no questions were addressed to the notifier.

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

Has evaluated this item in the context of the previous dossiers with Talimogene laherparepvec and has no further questions/comments in the context of the current application.

2. INFORMATION RELATED TO THE VECTOR
(e.g. description, sequence, mobilisation ...)

Comment

Has evaluated this item in the context of the previous dossiers with Talimogene laherparepvec and has no further questions/comments in the context of the current application.

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

Has evaluated this item in the context of the previous dossiers with Talimogene laherparepvec and has no further questions/comments in the context of the current application.

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

Has evaluated this item in the context of the previous dossiers with Talimogene laherparepvec and has no further questions/comments in the context of the current application.

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

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.

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

The biodistribution and shedding of intralesionally administered Talimogene laherparepvec are being investigated in a melanoma study. In this study, Talimogene laherparepvec DNA has been detected in blood, urine and samples from injected lesions. Infective virus has also been detected in samples from injected lesions.
Data concerning shedding following intrahepatic administration are not available. However, the probability of shedding in the blood and in urine is similar to that observed in previous dossiers (melanoma studies) and the probability of shedding in the injection site is lower to that observed during intralesional injection.

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

Has evaluated this item in the context of the previous dossiers with Talimogene laherparepvec and has no further questions/comments in the context of the current application.

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

Comment

Has evaluated this item in the context of the previous dossiers with Talimogene laherparepvec and has no further questions/comments in the context of the current application.

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

Comment

Has evaluated this item in the context of the previous dossiers with Talimogene laherparepvec and has no further questions/comments in the context of the current application.

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

Has evaluated this item in the context of the previous dossiers with Talimogene laherparepvec and has no further questions/comments in the context of the current application.

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

Has evaluated this item in the context of the previous dossiers with Talimogene laherparepvec and has no further questions/comments in the context of the current application.

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

Has evaluated this item in the context of the previous dossiers with Talimogene laherparepvec and has no further questions/comments in the context of the current application.

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

Has evaluated this item in the context of the previous dossiers with Talimogene laherparepvec and has no further questions/comments in the context of the current application.

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

Has evaluated this item in the context of the previous dossiers with Talimogene laherparepvec and has no further questions/comments in the context of the current application.

6.3. Information on the waste generated by the activity and its treatment.

(e.g. type of waste, amount ...)

Comment

Has evaluated this item in the context of the previous dossiers with Talimogene laherparepvec and has no further questions/comments in the context of the current application.

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

Comment

Has evaluated this item in the context of the previous dossiers with Talimogene laherparepvec and has no further questions/comments in the context of the current application.

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

Has not evaluated this item.

Comment SBB

These aspects have already been assessed in the context of previous dossiers with Talimogene laherparepvec.

7. OTHER INFORMATION

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

Comment

None

References

None

Bioveiligheidsraad
Conseil de Biosécurité

24-02-2015

Secretariaat
Secrétariat

O./ref.: WIV-ISP/41/BAC/2015_0113

Title: Advice of the Belgian Biosafety Advisory Council on the notification B/BE/14/BVW1 of the company Amgen for deliberate release in the environment of genetically modified organisms other than higher plants for research and development

Context

The notification B/BE/14/BVW1 has been submitted by Amgen to the Belgian Competent Authority in August 2014 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 and the title of the notification is: **"A Phase 2, Multicenter, Open-label, Single-arm Trial to Evaluate the Correlation Between Objective Response Rate and Baseline Intratumoral CD8+ Cell Density in Subjects With Unresected Stage IIIB to IVM1c Melanoma Treated with Talimogene laherparepvec"**.
The purpose of the release is a clinical trial to investigate the safety and efficacy of Talimogene laherparepvec in subjects with previously untreated, unresected, stage IIIb-IV melanoma.
Talimogene laherparepvec is an investigational medicinal product (IMP) developed for oncolytic immunotherapy. It is a recombinant herpes simplex type 1 virus (HSV-1) disabled by the functional deletion of two genes (ICP34.5 and ICP47) of the viral genome and genetically modified to express the human granulocyte macrophage colony-stimulating factor (hGM-CSF). Talimogene laherparepvec induces viral lysis of tumour cells and the expression of hGM-CSF stimulates a tumour-specific immune response.

Talimogene laherparepvec is administered by intralesional injection into cutaneous, subcutaneous, and nodal tumours. Multiple injections are foreseen until the patient has achieved a complete response to the treatment. The injection site is covered with an occlusive dressing but shedding from the treated tumour cannot completely be excluded knowing that viral replication in tumour tissue is possible. HSV-1 is an enveloped virus which is sensitive to and rapidly inactivated by both physical inactivation (dehydration, heat, low pH) and disinfectants (lipid solvents and mild detergents). It is a globally endemic pathogen of humans and has no known other natural host.

As the trial centres are located in Brussels, Flanders and Wallonia the national territory is considered as the potential release area of the rHSV-1.

The dossier has been officially acknowledged by the Competent Authority on 1 September 2014 and forwarded to the Biosafety Advisory Council for advice.
Within the framework of the evaluation procedure, the Biosafety Advisory Council, under the supervision of a coordinator and with the assistance of its Secretariat, contacted experts to evaluate the dossier. One experts from the common list of experts drawn up by the Biosafety Advisory Council (BAC) and the Biosafety and Biotechnology Unit (SBB) answered positively

to this request. The SBB also took part in the evaluation of the dossier while the Platform for Molecular Biology and Biotechnology of the Scientific Institute of Public Health evaluated the analytical procedure for the detection of rHSV-1 submitted by the notifier.
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 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 3 October 2014, 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 updated instructions for the personnel and for the patient, were received by the Competent Authority on 11 February 2015 and transmitted to the secretariat of the BAC on the same day. This complementary information was reviewed by the coordinator and the experts.

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 medicinal product and its safety for the treated patient, as well as aspects related to social, economical 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 one reaction of the public. The questions of the public tackling biosafety issues of the GMOs under consideration are taken in consideration in the opinion of the Biosafety Advisory Council. Answers to the questions of the public have been sent to the CA.

Summary of the Scientific evaluation

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

The donor, recipient and parental organisms have been correctly described in the dossier after additional information was requested and obtained from the notifier.

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

It is theoretically possible that individual recombination virions containing DNA with one copy of ICP34.5 and one copy of hGM-CSF could be generated.
In answers to questions of the experts the notifier evaluated the probability of occurrence and the consequences of these recombinations and convincingly demonstrated that the likelihood of such an event is low because it is unlikely that a wild-type virus would be in the same tissue as Talimogene laherparepvec in subjects since the latter is directly injected in tumour cells and cannot spread effectively into normal tissue, while a pre-existing HSV-1 would be in the mucosal tissues or neuronal ganglia of the patient. Furthermore, these variants are unstable and their virulence would not be restored to the levels of the wild-type HSV-1.

Recombinations of hGM-CSF with DNA sequences of the treated patient (host) could also occur. But the risk of homologous recombination between hGM-CSF and host sequences is negligible because DNA exchanges would be contained entirely within the hGM-CSF coding

sequence and possible consequences of such an event are negligible and the likelihood is low.

Expression of the hGM-CSF in a non-target host could have adverse health consequences by hindering the immune response but the notifier adequately argumented that Talimogene laherparepvec is engineered to replicate selectively in tumour tissue and expression of GM-CSF is limited to the injected tumour tissue. Absence of GM-CSF in serum has been demonstrated in a previous clinical trial.

For the experts it was not clear if Talimogene laherparepvec is able to reactivate endogenous wild-type HSV-1 during the establishment of a latent infection and if, in the long term, Talimogene laherparepvec is able to alter neuronal function. But the notifier notes that in previous clinical trials with this IMP incidences of HSV-1 infection in the treated patient are lower than the background rate in the general population. Possible reactivation of wild-type HSV-1 during and after treatment with Talimogene laherparepvec continues however to be studied extensively in ongoing clinical trials. In addition in pre-clinical studies, no evidence of virally-associated neuropathy has been observed in any animal treated with Talimogene laherparepvec.

3. The condition of release

The BAC had several criticisms relating to the measures to prevent inadvertent release of the GM product and the instructions prepared for the personnel. It was advised to reduce aerosol producing operations during preparation and administration of the GMO and to instruct personal manipulating the GMO to wear a mask. In addition the medical staff has to wear closed shoes in order to be protected against sharp and syringes that fall. Finally the internal transport of the vials containing the GMO should be performed in a hermetic transport box containing absorbent paper towels.
These remarks were taken into account by the notifier who updated the investigational product instruction manual and the information for healthcare personnel.

4. The risks for the environment and human health

Immune-compromised individuals are at potential risk to develop an infection if coming inadvertently into contact with the GMO. This was not discussed in the initial dossier. On request of the BAC the notifier has updated the Environmental risk assessment and in the amended instructions for the patient it is clearly stated that if patient's close contact or family member is pregnant or has a weakened immune system, they should not help when the injection sites have to be cleaned and the dressings have to be changed.

Related to the above point in case an immune-compromised person is inadvertently infected with the GMO the possibility exist that no obvious direct link is done with a patient treated with the GMO and will therefore not benefit of an adequate treatment. On request of the BAC the notifier has addressed this point and has committed to make available to all investigators in clinical trials with Talimogene laherparepvec the qPCR-based validated test to identify DNA of Talimogene laherparepvec in biological samples, including in swabs from lesions suspected to be herpetic in origin. Swabbing of any lesions suspected being herpetic in origin in patients, patients' close contacts, health care providers and caregivers for testing of Talimogene laherparepvec DNA, is part of the monitoring activities foreseen for this clinical trial.

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

Even if the risks are low some uncertainty remains (see above paragraphs 2 and 4). This stresses the importance of biosafety precautions to avoid unintended dissemination of the GMO that could lead to unknown adverse effects.
On request of the BAC the notifier amended the Investigational product instruction manual to ensure waste materials are incinerated even after decontamination and added detailed instructions in case of accidental spills or breakage of a vial containing the GMO.
The Accidental Spill information for Health care personnel could be further improved as suggested in Annex 1

In the dossier submitted by the notifier a detailed PCR protocol for the identification and detection of the GMO was lacking. The requested detailed protocol was submitted by the notifier on 11 February 2012 and it was considered adequate and sufficient by the GMO laboratory of the Scientific Institute of Public Health.

Conclusion

Based on the scientific assessment of the notification made by the Belgian experts, the Biosafety Advisory Council concludes that it is unlikely that Talimogene laherparepvec developed for oncolytic immunotherapy, 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.

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 safety instructions as described in the dossier also taking into account the suggestions from the Biosafety Advisory Council for improvement of the personnel instructions.

- 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.

- For the transport of the IMP the notifier should conform to the transportation rules regarding transport of GMO's.

- The Biosafety Advisory Council should be informed within 2 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 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 accidental releases, if any, of the recombinant HSV-1 .

Prof. M. De Proft
President of the Belgian Biosafety Advisory Council

Annex 1: Suggestions for improvement of the Accidental Spill information for Health care personnel
Annex 2: Compilation of comments of experts in charge of assessing the dossier B/BE/14/BVW1 (ref: BAC_2014_0647)

Annex 1
Suggestions for improvement of the Accidental Spill information for Health care personnel

Suggestion to improve the text after the third bullet:

In case you are involved in an accidental spill or breakage of a vial containing Talimogene Laherparepvec, please alert people in the area of the spill, remove all contaminated clothes and tell everybody to leave the area for 30 minutes.

As explanation for the 30 minutes between the spill and evacuation on one hand and the start of the clean-up it is suggested to add the following sentence in the text or as footnote:

In general, a 30-minute wait is sufficient for the droplets to settle and aerosols to be reduced by air changes but it depends on the number of air changes per hour. Longer waiting periods may be imposed depending on the situation.

Bioveiligheidsraad
Conseil de Biosécurité

03 October 2014

Secretariaat
Secrétariat

O./ref.: WIV-ISP/41/BAC_2014_0647
Email: BAC@wiv-isp.be

Compilation of Comments of Experts in charge of assessing the dossier B/BE/14/BVW1

Mandate for the Group of Experts: mandate of the Biosafety Advisory Council (BAC) of 24 June 2014
Coordinator: Prof. Jozef Anné (KUL)
Experts: Anton Roebroek (KUL), Aline Baldo (WIV-ISP, SBB)
Domains of expertise of experts involved:
Secretariat (SBB): Didier Breyer, Fanny Collard, Martine Goossens, Katia Pauwels

INTRODUCTION

Dossier **B/BE/14/BVW1** concerns a notification of the company Amgen Ltd 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 1 September 2014 and concerns a clinical trial with Talimogene laherparepvec a recombinant Herpes simplex virus 1. The herpes virus has been attenuated by the functional deletion of two genes (ICP34.5 and ICP47) of the HSV-1 genome and has been genetically modified to express granulocyte-macrophage colony-stimulating factor (GM-CSF). This GM-medication is developed for use as an oncolytic immunotherapy in melanoma patients.

♦ 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

Remark: The comments below have served as basis for a list of questions that the Competent authority forwarded on 03-10-2014 to the notifier with a request to provide additional information. The comments or remarks highlighted in grey correspond to the questions addressed to the notifier.

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.

Comment 2

In the “Technical and Scientific information on GMO”, fig 2 p 28, fig 4 p34 and fig 5 p35 : the figures do not correspond to the legend of fig 2, could the applicant indicate in these figures if the repeat sequences (R_L and R_S) are internal (IR_L and IR_S) or terminal (TR_L and TR_S)?
Could the applicant provide the studies 4647-00041 and 1182-00009?

Could the applicant explain why fragments of 17*syn*+ viral DNA were transferred into talimogene laherparepvec?

Additional comments from the coordinator

- The reference Mohr and Gluzman, 1996 does not describe what is mentioned in the figure (legend)
- The strain HSV-1 17syn+ is very well characterized (Bolovan et al, 1994) this clarifies why it has been used for the construction of talimogene laherparepvec.

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

Could the fragments of 17syn+ viral DNA and fragments of plasmid DNA have any consequences for the genetic stability of the final GMO?
Figure 6 page 41 is unreadable, could the applicant provide a larger version?
Could the applicant evaluate the consequences of recombinations of hGM-CSF with host sequences?
The applicant says p43 that “it is theoretically possible that individual recombination virions containing DNA with one copy of ICP34.5 and one copy of GM-CSF could be generated”. Even if these recombinants are not stable, could the applicant evaluate the consequences of this recombination and the probability of occurrence?

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

What are the consequences of expression of the hGM-CSF in a non target host? In the article of Harzstark and Small (2009), the authors say that “It is theorized that high doses of hGM-CSF may activate myeloid suppressor cells, create a counterproductive immune response. It is critical that the use of GM-CSF be optimized, in order to improve, rather than hinder, the immune response” Could hGM-CSF expressed in a non target host hinder the immune response?
Is talimogene laherparepvec able to reactivate endogenous wild-type HSV-1 during the establishment of a latent infection? Is talimogene laherparepvec able to alter neuronal function (long-term effect)?

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

Infection by HSV-1 virions occurs mainly by direct contact with the skin or mucous membranes, although transmission can also occur by inhalation of aerosols such as respiratory droplets (Lim et al., 2013). Aerosol producing operations should be reduced during preparation and administration of the GMO and personal manipulating the GMO should wear a mask because the puncture of a contained holding vector may produce aerosols. The medical staff should also wear closed shoes in order to be protected against sharp and syringes that fall.
The internal transport of the vials containing the GMO should be performed in an hermetic transport box containing absorbent paper towels.
Transportation (p. 74 of the technical dossier): The medicinal product containing GMO should be considered as a "Miscellanous dangerous Goods", Class 9 for the International Air Transport Association (IATA): "Miscellaneous dangerous goods are substances and articles which during transport present a danger or hazard not covered by other classes. This class encompasses, but is not limited to, environmentally hazardous substances, substances that are transported at elevated temperatures, miscellaneous articles and substances, **genetically modified organisms** and micro-organisms and (depending on the method of transport) magnetized materials and aviation regulated substances.

Additional comments SBB
When multiple lesions are treated it is not clear in the dossier if its needed to put each time a new needle on the syringe.

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

ERA, 2.1.2.5.2 Effects in Immune-compromised Individuals (page 30-31)
In case an immunocompromised person will be infected with Talimogene Laherparepvec there is the possibility that there is no obvious direct link with a treatment with or a patient treated with Talimogene Laherparepvec. So specific testing for Talimogene Laherparepvec is not considered. Are the normal tests for HSV-1 diagnosis suitable to identify a Talimogene Laherparepvec infection as an HSV-1 infection resulting in treatment with e.g. acyclovir or is there any danger that in such a case a Talimogene Laherparepvec infection will be missed and no acyclovir treatment will be started.

Comment 2

Could the applicant evaluate the possible effects if an immunocompromised person comes into contact with the GMO?

Additional comment SBB
In the instructions for the patient it should be clearly stated that he should avoid ANY contact with immunocompromised persons.

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 evaluated this item and has no questions/comments.

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

Has evaluated this item and has no questions/comments.

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

The applicant says that "**If possible**, materials deriving from healthcare activities should not be discarded in landfills even after decontamination." They should **never been discarded in landfills**, they should be incinerated even after decontamination.

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

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Strict procedures should be provided for medical staff and persons in contact with the patient during the release of the viral vector. These procedures should be posted in the hospital room where the treatment should take place.
A spill kit should be available in the facility, this spill kit should contain appropriate disinfectant, personal protective equipment (PPE, i.e. gloves, safety glasses, laboratory coat, mask), tongs or forceps in order to take broken vials, absorbent paper towels, biohazard waste bags.
In case of accidental spills or breakage of a vial containing the GMO, the medical staff should alert people in the area of the spill, remove contaminated clothes and leave the area for 30 min. He should close the area and post "DO NOT ENTER". After 30 min, he must wear a clean lab coat and wear gloves, glasses and a mask. He must cover the spill with towels and other absorbent material starting from the edge toward the centre. He must carefully pour the appropriate disinfectant over the absorbent material starting from the edge to the centre. It must allow a sufficient contact time for the

disinfectant to inactivate the GMO. After that, he must remove the paper towels and broken vials with tongs or forceps and discard in a biohazard waste bag. The PPE should be discard in the biohazard bag. The lab coat should be decontaminated before disposal. The medical staff should report the incident to the responsible of the site.

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

See also 5.2.
Technical and Scientific information on the GMO (page 48-50)
f) Description of identification and detection techniques including techniques for the identification and detection of the inserted sequence and vector
g) Sensitivity, reliability (in quantitative terms) and specificity of detection and identification techniques

Is there any risk, that a Talimogene Laherparepvec infection is not recognized as a HSV-1-like infection in standard HSV-1 diagnosis tests?

Additional comment SBB:
According to the Royal Decree of 21 February 2005, the notifier is requested to provide in the notification a description of identification and detection techniques, including information on sensitivity, reliability and specificity of these techniques. The submitted dossier lacks a detailed PCR protocol for the identification and detection of the GMO.

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

ERA 2.1.2.4.2 Clinical Safety Data Obtained with Talimogene Laherparepvec (page 29-30)
Several clinical trials using Talimogene Laherparepvec are already conducted. The most commonly reported treatment-related adverse events in patients are listed and apparently considered not to be prohibitive objections against the use of Talimogene Laherparepvec. As the dose of Talimogene Laherparepvec used in these previous studies is not mentioned nor compared with the proposed dose in the present study the suggested conclusions are not justified unless the additional information is provided stating that the doses are similar/comparable.

Additional comment SBB:
The aspects concerning the safety of the medicinal product for the treated patient are outside the scope of this evaluation

References

Bolovan CA, Sawtell NM, Thompson RL. ICP34.5 mutants of herpes simplex virus type 1 strain 17syn+ are attenuated for neurovirulence in mice and for replication in confluent primary mouse embryo cell cultures. *Journal of virology*. 1994;68:48-55.

Harzstark AL, Small EJ. Immunotherapeutics in development for prostate cancer. *Oncologist*, 2009, 4, 391-8.

Lim F., Khalique H, Ventosa M, Baldo A. Biosafety of gene therapy vectors derived from Herpes simplex virus type 1. *Curr Gene Ther*, 2013, 13, 478-91.

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Conseil de Biosécurité

12-10-2015

Secretariaat
Secrétariat

O./ref.: WIV-ISP/41/BAC/2015_0679

Title: Advice of the Belgian Biosafety Advisory Council on the notification B/BE/15/BVW1 of the company Amgen for deliberate release in the environment of genetically modified herpes simplex type 1 virus (HSV-1) for research and development

Context

The notification B/BE/15/BVW1 has been submitted by Amgen to the Belgian Competent Authority in July 2015 for a request of deliberate release in the environment of genetically modified organisms (GMO) 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 and the title of the notification is: **"A Phase 1b/3, Multicenter, Open-label Trial of Talimogene Laherparepvec in Combination With Pembrolizumab (MK-3475) for Treatment of Unresected, Stage IIIB to IVM1c Melanoma"**. The clinical trial aims at investigating whether a regimen of an oncolytic immunotherapy (Talimogene laherparepvec) and a monoclonal antibody (pembrolizumab) is safe and tolerable, and whether the combined treatment might enhance the clinical efficacy shown when pembrolizumab is administered alone to subjects with previously untreated, unresected, stage IIIB to IVM1c melanoma.
Talimogene laherparepvec is an investigational medicinal product (IMP) developed for oncolytic immunotherapy. It is a recombinant herpes simplex type 1 virus (HSV-1) attenuated by the functional deletion of two genes (ICP34.5 and ICP47) of the viral genome and genetically modified to express the human granulocyte macrophage colony-stimulating factor (hGM-CSF). Talimogene laherparepvec induces viral lysis of tumour cells and the expression of hGM-CSF stimulates a tumour-specific immune response.

Talimogene laherparepvec is administered by intralesional injection into cutaneous, subcutaneous, and nodal tumours. Multiple injections are foreseen until the patient has achieved a complete response to the treatment. The injection site is covered with an occlusive dressing but shedding from the treated tumour cannot be completely excluded knowing that viral replication in tumour tissue is possible. HSV-1 is an enveloped virus which is sensitive to and rapidly inactivated by both physical inactivation (dehydration, heat, low pH) and disinfectants (lipid solvents and mild detergents). It is a globally endemic pathogen of humans and has no known other natural host.

As the trial centres are located in Brussels, Flanders and Wallonia the national territory is considered as the potential release area of the rHSV-1.

The dossier has been officially acknowledged by the Competent Authority on 17 July 2015 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. Since Talimogene laherparepvec had already been assessed by the BAC in the

framework of a previous clinical trial (notification B/BE/14/BVW1)[1] the same experts who evaluated this previous dossier were contacted and took part in the evaluation.

The experts assessed whether the information provided in the notification was sufficient and accurate in order to state that the deliberate release of the GMO 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) in the context of the intended use. Since the characteristics of the GMO had already been assessed in the framework of the evaluation of the notification B/BE/14/BVW1, the assessment of the current notification focused on the specific conditions of the release as foreseen in this new clinical trial protocol. See Annex I for an overview of all the comments from the experts.

The analytical procedure for the detection of rHSV-1 had already been submitted in the framework of notification B/BE/14/BVW1 and evaluated at that time by the Platform Biotechnology and Molecular Biology of the Scientific Institute of Public Health. .

On 24 August 2015, based on a list of questions prepared by the BAC, the Competent Authority requested the notifier to provide additional information. The answers to these questions, including updated instructions for the personnel and for the patient, were received by the Competent Authority on 16 September 2015 and transmitted to the BAC on the same day. This complementary information was reviewed by the coordinator and the experts and considered sufficient.

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 IMP and its safety for the treated patient, 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 no reaction from the public.

Summary of the Scientific evaluation

1. Characteristics of the donor, recipient or parental organism

See advice of the BAC on the notification B/BE/14/BVW1 (Annex 2).

2. Characteristics of the GMO and of the medication

See advice of the BAC on the notification B/BE/14/BVW1 (Annex 2).

3. Conditions of release

In the framework of the evaluation of the notification B/BE/14/BVW1 the BAC had several criticisms relating to the measures to prevent inadvertent release of the GMO and the instructions prepared for the personnel. It was advised to instruct personnel manipulating the GMO to wear a mask and closed shoes, and to perform the internal transport of the vials containing the GMO in a hermetic transport box containing absorbent paper towels.

[1] Advice on the notification B/BE/14/BVW1 of 24 February 2015 (ref BAC_2015_0113) – see Annex 2

These remarks were taken into account by the notifier in this new dossier but not in all parts of the dossier. On request of the BAC the notifier updated the Investigational Product Instruction Manual and the information for healthcare personnel accordingly.

4. Potential risks for the environment, animal or human health associated with the release of the GMO

On request of the BAC the notifier provided an assessment of the potential impact of the combined application of Talimogene laherparepvec and the monoclonal antibody pembrolizumab compared to the application of Talimogene laherparepvec alone. Based on this additional information the BAC agrees with the notifier that the application of pembrolizumab will have no impact on the replication of Talimogene laherparepvec in melanoma and non-melanoma cells and subsequent shedding of the viral vector. Hence the combined application of Talimogene laherparepvec and pembrolizumab does not increase the risk for the environment and human health in comparison to the application of Talimogene laherparepvec alone.

As a result of the evaluation of the notification B/BE/14/BVW1 the notifier was requested to clearly indicate in the instructions for the patient that if a patient's close contact or family member is pregnant or has a weakened immune system, this person should not help when the injection sites have to be cleaned and the dressings have to be changed. This request was taken into account by the notifier in the current notification but not in all parts of the dossier. On request of the BAC the notifier updated the Healthcare information sheet accordingly.

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

As in the previous trial, the monitoring activities foreseen for this clinical trial cover swabbing of any lesions suspected being herpetic in origin in patients, patients' close contacts, health care providers and caregivers for testing of Talimogene laherparepvec DNA.

On request of the BAC the notifier amended the Investigational Product Instruction Manual to ensure that waste materials are incinerated after decontamination.

Conclusion

Based on the scientific assessment made by the Belgian experts, the Biosafety Advisory Council concludes that it is unlikely that Talimogene laherparepvec developed for oncolytic immunotherapy in combination with pembrolizumab, 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.

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 safety instructions as described in the dossier.

- 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 authorisations 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.

- For the transport of the IMP the notifier should conform to the transportation rules regarding transport of GMO's.

- The Biosafety Advisory Council should be informed within 2 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 Council a report with details concerning the biosafety aspects of the project. This report shall contain at least:
    - 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 accidental releases, if any, of the recombinant HSV-1.

Prof. M. De Proft
President of the Belgian Biosafety Advisory Council

Annex 1: Compilation of comments of experts in charge of assessing the notification B/BE/15/BVW1 (ref: BAC_2015_0554)
Annex 2: Advice of the Belgian Biosafety Advisory Council on the notification B/BE/14/BVW1 of the company Amgen for deliberate release in the environment of genetically modified organisms other than higher plants for research and development (ref. BAC_2015_0113)

Bioveiligheidsraad
Conseil de Biosécurité

25 August 2015

Secretariaat
Secrétariat

O./ref.: WIV-ISP/41/BAC_2015_0554
Email: BAC@sbb.ihe.be

Compilation of Comments of Experts in charge of assessing the dossier B/BE/15/BVW1

Mandate for the Group of Experts: mandate of the Biosafety Advisory Council (BAC) of 16 June 2015
Coordinator: Prof. Jozef Anné (KUL)
Experts: Anton Roebroek (KUL), Aline Baldo (WIV-ISP, SBB)
Domains of expertise of experts involved: Molecular genetics, virology, biosafety, contained use
Secretariat (SBB): Didier Breyer, Fanny Coppens, Martine Goossens, Katia Pauwels

INTRODUCTION

Dossier **B/BE/15/BVW1** concerns a notification of the company Amgen Ltd 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 17/07/2015 and concerns a clinical trial with Talimogene laherparepvec a recombinant Herpes simplex virus 1. The herpes virus has been attenuated by the functional deletion of two genes (ICP34.5 and ICP47) of the HSV-1 genome and has been genetically modified to express granulocyte-macrophage colony-stimulating factor (GM-CSF). The intended therapeutic strategy is to produce a direct oncolytic effect by replication of the virus within the tumour, and induction of an anti-tumour immune response, enhanced by the local expression of hGM CSF.
Talimogene laherparepvec was already notified by Amgen in August 2014 in dossier B/BE/14/BVW1.

♦ 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

Remark: The comments below have served as basis for a list of questions that the Competent authority forwarded on 24-08-2015 to the notifier with a request to provide additional information. The comments or remarks highlighted in grey correspond to the questions addressed to the notifier.

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.

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

Infection by HSV-1 virions occurs mainly by direct contact with the skin or mucous membranes, although transmission can also occur by inhalation of aerosols such as respiratory droplets (Lim *et al.*, 2013). Aerosol producing operations should be reduced during preparation and administration of the GMO and personal manipulating the GMO should wear a mask because the puncture of a vial holding the vector may produce aerosols. The medical staff should also wear closed shoes in order to be protected against sharp and syringes that fall.
The internal transport of the vials containing the GMO should be performed in a hermetic transport box containing absorbent paper towels.

Comment SBB

The above comment was already raised in the frame of the evaluation of notification B/BE/14/BVW1.

The remark has been taken into account by the notifier in this new dossier (see Investigational-Product Instruction Manual) but not in every part of the dossier.

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

The dossier parts Technical and Scientific information on the GMO and Environmental Risk Assessment of Talimogene Laherparepvec in the present dossier B/BE/15/BVW1 largely overlaps with the revised dossier parts Technical and Scientific information on the GMO and Environmental Risk Assessment of Talimogene Laherparepvec in the dossier B/BE/14/BVW1. The revised version of the dossier B/BE/14/BVW1 obtained finally a positive advice by the Biosafety Advisory Counsel. The present dossier B/BE/15/BVW1 deals with a comparative clinical study conducting a phase 1b/3, multicenter, open-label trial to evaluate the safety and efficacy of talimogene laherparepvec and pembrolizumab compared to pembrolizumab alone in subjects with previously untreated, unresected, stage IIIb-IVM1c melanoma.

In the Environmental Risk Assessment of Talimogene Laherparepvec in the present dossier B/BE/15/BVW1, however, no assessment is made concerning the potential impact of the combined application of talimogene laherparepvec and pembrolizumab compared to application of talimogene laherparepvec alone with respect to the risk for the environment and human health. The additional application of pembrolizumab should be discussed and evaluated in comparison with application of talimogene laherparepvec alone. It should be discussed that additional application of pembrolizumab is not expected to have any impact at all on the replication of talimogene laherparepvec in melanoma and non-melanoma cells and subsequent shedding etc. and subsequently on the risk for the environment and human health in comparison to talimogene laherparepvec alone.

Comment 2

Could the applicant provide the following reference: Andtbacka RH, Kaufman HL, Collichio F et al., Talimogene Laherparepvec improves durable response rate in patients with advanced melanoma. J Clin Onc 2015.

Comment SBB:

The coordinator forwarded a copy of the article to the expert who didn't have any additional comment or questiont.

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

Pregnant women have a weakened immune system, therefore they should not come in contact with a talimogene laherprepvec injection site or its protective dressing and should not help when the injection sites have to be cleaned and the dressings have to be changed.
Personnel administrating talimogene laherprepvec should wear a mask, it should be added in the talimogene laherprepvec safety data sheet.

CommentSBB:
Instructions for pregnant women are correctly given in the 'Information sheet for caregivers, family members or other close contacts' but it should also be clearly written in the Investigational-Product Instruction Manual and in the Safety Data Sheet.
The above comment was already raised in the frame of the evaluation of notification B/BE/14/BVW1.
The remark has been taken into account by the notifier in this new dossier (see Investigational-Product Instruction Manual) but not in the Safety Data Sheet.

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 evaluated this item and has no questions/comments.

Comment 2

Has evaluated this item and has no questions/comments.

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

Has evaluated this item and has no questions/comments.

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

In the environmental risk assessment the applicant says that "If possible, material deriving from healthcare activities should not be discarded in landfills even after decontamination." For safety reasons, they should never been discarded in landfills, but should be incinerated even after decontamination.

Contaminated protective dressing must not be discarded in landfills, it must return to the facility and it must be incinerated, it should be added in the information sheet for caregivers, family members or other close contacts to clinical trial participants.

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

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Sodium hypochlorite is unstable, diluted solutions (1% sodium hypochlorite) should be prepared extemporaneously, dated and used rapidly (within the week). It should be stored in the dark and protected from heat.

Comment coordinator:

If stored in ideal conditions stabilized sodium hypochlorite solutions remain stable for several months (Fabian TM &,Walker SE, 1982). But agree with the expert that traceability of those strict conditions is not easy and it is always safer to use the prepared solution within the week.

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.

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

Both the dossier parts Technical and Scientific information on the GMO (page 62) and Environmental Risk Assessment (page 30) of Talimogene Laherparepvec in the present dossier B/BE/15/BVW1 have short passages where the abbreviation/short name T-VEC (not is the list of abbreviations) is used instead of the full name talimogene laherparepvec. To avoid any confusion T-VEC should be replaced by talimogene laherparepvec.

In the Environmental Risk Assessment of Talimogene Laherparepvec in the present dossier B/BE/15/BVW1 the first sentence at the top of page 53 is double.

Comment 2

Could the applicant explain why the GMO (talimogene laherparepvec) must be administered before MK-3475 when they are administered on the same day?

References

Fabian TM, Walker SE. Stability of sodium hypochlorite solutions., Am J Hosp Pharm. 1982 Jun;39(6):1016-7.

Lim F, Khalique H, Ventosa M, Baldo A. Biosafety of gene therapy vectors derived from Herpes simplex virus type 1. *Curr Gene Ther*, 2013, 13, 478-91.

Bioveiligheidsraad
Conseil de Biosécurité

12-01-2016

Secretariaat
Secrétariat

O./ref.: WIV-ISP/41/BAC_2016_0023

Title: Advice of the Belgian Biosafety Advisory Council on the notification B/BE/15/BVW2 of the company Amgen for deliberate release in the environment of genetically modified herpes simplex type 1 virus (HSV-1) for research and development

Context

The notification B/BE/15/BVW2 has been submitted by Amgen to the Belgian Competent Authority in November 2015 for a request of deliberate release in the environment of genetically modified organisms (GMO) 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 and the title of the notification is: **"A Phase 1b/3, Multicenter, Open-label Trial of Talimogene Laherparepvec in Combination With Pembrolizumab (MK-3475) for Treatment of Subjects With Recurrent of Metastatic Squamous Cell Carcinoma of the Head and Neck"**. The clinical trial aims at investigating whether a regimen of an oncolytic immunotherapy (Talimogene laherparepvec) and a monoclonal antibody (pembrolizumab) is safe and tolerable, and whether the combined treatment might enhance the clinical efficacy shown when pembrolizumab is administered alone to subjects with recurrent metastatic squamous cell carcinoma of the head and neck.

Talimogene laherparepvec is a recombinant herpes simplex type 1 virus (HSV-1) attenuated by the functional deletion of two genes (ICP34.5 and ICP47) of the viral genome and genetically modified to express the human granulocyte macrophage colony-stimulating factor (hGM-CSF). The therapeutic strategy of Talimogene laherparepvec is to allow replication of the recombinant virus within the tumour, to induce viral lysis of tumour cells and to induce an anti-tumour immune response enhanced by the local expression of hGM-CSF.

Talimogene laherparepvec is administered by intralesional injection into cutaneous, subcutaneous, and nodal tumours. Multiple injections are foreseen until the patient has achieved a complete response to the treatment. The injection site is covered with an occlusive dressing but shedding from the treated tumour cannot be completely excluded due to viral replication in tumour tissue. HSV-1 is an enveloped virus which is sensitive to and rapidly inactivated by both physical inactivation (dehydration, heat, low pH) and disinfectants (lipid solvents and mild detergents). It is a globally endemic pathogen of humans and has no known other natural host.

The trial centres are located in Brussels and in Flanders. The national territory is considered as the potential release area of the rHSV-1.

The dossier has been officially acknowledged by the Competent Authority on 19 November 2015 and forwarded to the Biosafety Advisory Council (BAC) for advice.
On 22 October 2015 EMA recommended Imlygic (active substance Talimogene laherparepvec) for approval for EU marketing authorisation with the indication of treatment of certain stages of melanoma[1]. The therapeutic strategy of the current clinical trial aims the treatment of subjects with recurrent metastatic squamous cell carcinoma of the head and neck, thereby justifying an evaluation of elements for the environmental risk assessment in the context of the current dossier.
Within the framework of the evaluation procedure, the BAC, under the supervision of a coordinator and with the assistance of its Secretariat, contacted one expert to evaluate the dossier, taking into account that Talimogene laherparepvec had already been assessed by the BAC in the framework of two previous notifications (B/BE/14/BVW1 and B/BE/15/BVW1)[2,3].
The expert assessed whether the information provided in the notification was sufficient and accurate in order to state that the deliberate release of the GMO 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) in the context of the intended use. Since the characteristics of the GMO had already been assessed previously, the assessment of the current notification focused on the specific conditions of the release taking into account the change of indication. See Annex I for an overview of the comments of the expert.

The analytical procedure for the detection of rHSV-1 had already been submitted in the framework of notification B/BE/14/BVW1 and evaluated at that time by the Platform Biotechnology and Molecular Biology of the Scientific Institute of Public Health.

The scientific evaluation has been performed considering the 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 Investigational Medicinal Product (IMP) and its safety for the treated patient, 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 one comment from the public partly dealing with biosafety, which has been considered by the BAC in the preparation of the current advice.

[1] http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002771/smops/Positive/human_smop_000894.jsp&mid=WC0b01ac058001d127
[2] Advice on the notification B/BE/14/BVW1 of 24 February 2015 (ref BAC_2015_0113) – see Annex 2
[3] Advice on the notification B/BE/15/BVW2 of 12 October 2015 (ref BAC_2015_0679) – see Annex 2

Summary of the scientific evaluation

1. Characteristics of the donor, recipient or parental organism

See advice of the BAC on the notification B/BE/14/BVW1 (Annex 2).

2. Characteristics of the GMO and of the medication

See advice of the BAC on the notification B/BE/14/BVW1 (Annex 2).

3. Conditions of release

In the framework of the evaluation of the notification B/BE/14/BVW1 the BAC had several criticisms relating to the measures to prevent inadvertent release of the GMO and the instructions prepared for the personnel. It was advised to instruct personnel manipulating the GMO to wear a mask and closed shoes, and to perform the internal transport of the vials containing the GMO in a hermetic transport box containing absorbent paper towels.
These remarks were taken into account by the notifier in this new dossier by providing a country-specific addendum to the Investigational Product Instruction Manual (IPIM) and by adapting the Healthcare information sheet accordingly.

4. Potential risks for the environment, animal or human health associated with the release of the GMO

It was noted that the first dose of Talimogene laherparepvec was increased up to 8.0 mL of 10^6 PFU/mL compared to two subsequent injections of 4.0 mL of 10^6 PFU/mL as described in the previous notification (B/BE/15/BVW1). The BAC is of the opinion that the increased dose with the first injection as described in the current dossier does not affect biodistribution nor shedding in terms of increased risk for the environment and human health.
With regard to the administration of corticosteroids in the context of adapted treatment related to toxic effects upon administration of talimogene laherparepvec combined with pembrolizumab (also described in the context of notification B/BE/15/BVW1), the BAC is of the opinion that it is unlikely that it will have adverse effects on human health or the environment.
It was also noted that the notifier took into account the remarks of the BAC addressed in the context of the notification B/BE/14/BVW1, thereby providing clear instructions for patient's close contacts or family members who are pregnant or have a weakened immune system.

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

As in the previous notification (B/BE/15/BVW1), the monitoring activities foreseen for this clinical trial cover swabbing of any lesions suspected to be of herpetic origin in patients, patients' close contacts, health care providers and caregivers for testing of Talimogene laherparepvec DNA. Waste materials will be incinerated after decontamination.

Conclusion

Based on the scientific assessment of this dossier made by the Belgian expert, taking into account the previous advices on notifications B/BE/14/BVW1 and B/BE/15/BVW1, and considering the data presently available, the Biosafety Advisory Council concludes that it is unlikely that Talimogene laherparepvec developed for oncolytic immunotherapy in combination with pembrolizumab, will have any adverse effects on human health or the environment in the context of the intended clinical trial and provided that all the foreseen safety measures are followed.

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 safety instructions as described in the dossier.
- 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 authorisations 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 the contained use of genetically modified micro-organisms.
- For the transport of the IMP the notifier should conform to the transportation rules regarding transport of GMOs.
- The BAC 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 the competent authority for the attention of the BAC a report with details concerning the biosafety aspects of the project. This report shall contain at least:
  - 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 accidental releases, if any, of the recombinant HSV-1.

Prof. M. De Proft
President of the Belgian Biosafety Advisory Council

Annex 1: Compilation of comments of the experts in charge of assessing the notification B/BE/15/BVW2 (ref: BAC_2015_0838)

Annex 2: Advice of the Belgian Biosafety Advisory Council on the notification B/BE/15/BVW1 of the company Amgen for deliberate release in the environment of genetically modified organisms other than higher plants for research and development (ref. BAC_2015_0679) and Advice of the Belgian Biosafety Advisory Council on the notification B/BE/14/BVW1 of the company Amgen for deliberate release in the environment of genetically modified organisms other than higher plants for research and development (ref. BAC_2015_0113)

Bioveiligheidsraad
Conseil de Biosécurité

18 December 2015

Secretariaat
Secrétariat

O./ref.: WIV-ISP/41/BAC_2015_0838
Email: bac@wiv-isp.be

Compilation of comments of experts in charge of assessing the dossier B/BE/15/BVW2

Mandate for the Group of Experts: Mandate of the Biosafety Advisory Council (BAC) of 13 November 2015
Coordinator: Prof. Jozef Anné (KUL)
Experts: Aline Baldo (WIV-ISP, SBB)
Domains of expertise of experts involved: Molecular genetics, virology, biosafety, contained use
Secretariat (SBB): Didier Breyer, Fanny Coppens, Katia Pauwels

INTRODUCTION

Dossier **B/BE/15/BVW2** concerns a notification of the company Amgen Ltd 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 19 November 2015 and concerns a clinical trial with Talimogene laherparepvec, a recombinant Herpes simplex virus 1. The herpes virus has been attenuated by the functional deletion of two genes (ICP34.5 and ICP47) of the HSV-1 genome and has been genetically modified to express granulocyte-macrophage colony-stimulating factor (GM-CSF). The intended therapeutic strategy is to produce a direct oncolytic effect by replication of the virus within the tumour, and induction of an anti-tumour immune response, enhanced by the local expression of hGM CSF. The clinical trial aims at investigating whether a regimen of Talimogene laherparepvec and a monoclonal antibody (pembrolizumab), a combined treatment that was already notified by Amgen in dossier B/BE/15/BVW1 (July 2015), might enhance the clinical efficacy when administered to subjects with recurrent metastatic squamous cell carcinoma of the head and neck (new indication compared to dossier B/BE/15/BVW1).
Talimogene laherparepvec was also already notified by Amgen in September 2014 in dossier B/BE/14/BVW1.

♦ 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

Remark: Based on the comments and remarks below, no questions were addressed to the notifier.

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

Has evaluated this item and has no questions/comments.

2. INFORMATION RELATED TO THE VECTOR

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

Comment

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

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

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

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

The maximal volume of talimogene laherparepvec that could be administrated at any treatment is 8 ml. In the previous dossier 4 ml maximal was injected. Does the applicant explain the consequences of a double dose of talimogene laherparepvec in term of biodistribution and shedding and subsequently on the risk for the environment and human health?

Comment coordinator

Will 1.10^6 make a difference with 2.10^6 in terms of bio-distribution and shedding? Personally I don't think it will. Later on 10^8 pfu is used in both cases. In the protocol of previous notification: "*Talimogene LaherparepvecUp to 4 mL106 PFU/mL at Day 1 followed by 108 PFU/mL 21 (+5) days later, then every 14 (±3) days*"

Comment 2

Does the administration of corticosteroïde have any impact on the replication of talimogene laherparepvec in the tumors and subsequent shedding and subsequently on the risk for the environment and human health in comparison to talimogene laherparepvec alone?

Comment SBB

The administration of corticosteroids has been described by the notifier in the context of adapted treatment related to toxic effects upon administration of talimogene laherparepvec combined with pembrolizumab and was also described in the context its previous notification (B/BE/15/BVW1). However, this element did not give raise to any question by the experts in the context of the previous notification.

Comment coordinator

Randomized clinical trials have not shown an increase in viral dissemination in any patients treated with corticosteroids when compared with a control group. The only trial in which dissemination was reported included 201 patients randomized to receive combinations of acyclovir, prednisone, and placebo. One patient in the acyclovir-placebo group and two patients in the prednisone-placebo group developed cutaneous dissemination, all of which resolved without further complications (LL MacFarlane - 1998)

Spruance SL and McKeough MB (2000) conclude that the use of topical corticosteroids in combination with an antiviral agent appears to significantly improve the clinical course of recurrent herpes labialis infection, with only minor adverse reactions. The authors do caution, however, that theirs was a pilot

study, and that more research is needed to confirm their findings. *(Am Fam Physician.* 2000 Dec 1;62(11):2514). http://www.aafp.org/afp/2000/1201/p2514.html
Alfar MY et al. 2015 conclude that systemic corticosteroids as a treatment modality should always be considered for the treatment of erythema multiforme minor.

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

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

Has evaluated this item and has no questions/comments.

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

Comment

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

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

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

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

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

Has evaluated this item and has no questions/comments.

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

Has evaluated this item and has no questions/comments.

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

Comment

Has evaluated this item and has no questions/comments.

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

Comment

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

Has not evaluated this item.

7. OTHER INFORMATION

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

Comment

None

References

Alfar MY, AlRousan M, Almajali Z, Batarseh E, Alsaddi R. The use of corticosteroids in management of Herpes associated Erythema Multiforme. *J Pak Med Assoc*. 2015; 65(12): 1351-3.

MacFarlane et al. The use of corticosteroids in the management of Herpes. *JABFP*, 1998, 11(3), 224-228.

Spruance SL, McKeough MB. Combination treatment with famciclovir and a topical corticosteroid gel versus famciclovir alone for experimental ultraviolet radiation–induced herpes simplex labialis: a pilot study. *J Infect Dis*. 2000, 181, 1906–10.