Adviesraad voor Bioveiligheid
Conseil consultatif de Biosécurité

Advice of the Belgian Biosafety Advisory Council on the notification B/BE/21/BVW7 of the company Boehringer Ingelheim, for deliberate release in the environment of genetically modified organisms other than higher plants for research and development

03/06/2022
Ref. SC/1510/BAC/2022_0705

Context

The notification B/BE/21/BVW7 has been submitted by SCS Boehringer Ingelheim Ltd. to the Belgian Competent Authority in December 2021 for a request of deliberate release in the environment of genetically modified organisms (GMOs) 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: ***"Phase I open-label, dose escalation trial of BI 1831169 monotherapy and in combination with ezabenlimab in patients with advanced or metastatic solid tumors".***

The purpose of this study is to evaluate the safety, the efficacy and the recommended dose for BI 1831169 both as monotherapy and in combination with ezabenlimab (anti-PD-1) when given via intravenous and/or intratumoral routes in participants with advanced or metastatic solid tumors.

The investigational medicinal product (IMP), BI 1831169, is a recombinant chimeric oncolytic vesicular stomatitis virus (VSV) of the Indiana strain carrying the envelope glycoprotein (GP) of the visceral non-neurotropic WE-HPI strain of the lymphocytic choriomeningitis virus (LCMV; Arenaviridae family), instead of its natural wild-type glycoprotein (G). The GP of the LCMV abrogates neurotoxicity in mice even after direct injection of high doses directly into the brain (Muik *et al*., 2014).

Based on the lower type I IFN-associated antiviral potential of cancer cells compared to normal cells, oncolytic viruses (OVs) have the ability to selectively replicate in and lyse tumor cells as well as to stimulate adaptive immune responses directed against the tumor (S.A.Felt *et al*., 2017).

A Muik *et al*., Re-engineering vesicular stomatitis virus to abrogate neurotoxicity, circumvent humoral immunity, and enhance oncolytic potency, Cancer Res. 2014 Jul 1;74(13):3567-78

S.A.Felt *et al*., Recent advances in vesicular stomatitis virus-based oncolytic virotherapy: a 5-year update, J Gen Virol. 2017 Dec; 98(12): 2895–2911

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Due to the ubiquitous expression of the low density lipoprotein receptors which serve as a major entry receptor for VSV, the virus is able to infect a lot of animal cells (D. Finkelshtein *et al*., 2013).
Taken together, VSV-GP has a beneficial toxicity profile with an expected high efficacy against a large variety of tumors.

Overall, approximately 115 patients will be included in this Phase I study, with 4 expected to be enrolled in Belgium. The trial is split into two parts. Part 1 investigates the use of VSV-GP (BI 1831169) as a monotherapy via three different routes of administration: intratumorally (i.t.), intravenously (i.v.) and as a combination of i.t. and i.v. Part 2 follows Part 1 to investigate the use of VSV-GP in combination with a checkpoint inhibitor (anti-PD1) ezabenlimab which is given intravenously. The oncolytic virus, VSV-GP is given 5 times on Day 1, Day 4, Day 22, Day 43 and Day 64. In Part I, BI 1831169 will be tested at $5x10^7$, $5x10^8$, and $5x10^9$ Median Tissue Culture Infectious Dose ($TCID_{50}$) in Arm A (i.t.) and at doses of $5x10^8$, $5x10^9$, and $5x10^{10}$ $TCID_{50}$ in Arm B (i.v.) and C (combined i.t.and i.v.). In Part II, in each arm (D, E and F), BI 1831169 will be tested initially at one dose level less than the mRP2D dose for the corresponding arm in Part 1.

This study will be conducted at one clinical site located in Brussels.

The virus shedding will be assessed in buccal swabs, nasal swabs, i.v./i.t. administration site swabs and urine samples, collected from all patients that have received BI 1831169 at all visits until the end of treatment visit (26 days after last dose of IMP).

The dossier has been officially acknowledged by the Competent Authority on 06 January 2022 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. Three experts from the common list of experts drawn up by the BAC and the Service Biosafety and Biotechnology (SBB) of Sciensano answered positively to this request. The SBB also took part in the evaluation of the dossier. The experts 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 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 its intended use. See Annex I for an overview of all the comments from the expert.

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, economic or ethical considerations, are outside the scope of this evaluation.

D. Finkelshtein *et al*. LDL receptor and its family members serve as the cellular receptors for vesicular stomatitis virus. Proc. Natl Acad. Sci. USA 110, 7306–7311 (2013)

On 7 February 2022, 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 were received by the Competent Authority on 11 April 2022 and transmitted to the secretariat of the BAC on the same day. This complementary information was reviewed by the BAC and resulted in a second list of questions, which was transmitted to the notifier on 02 May 2022. The answers of the notifier were received on 23 may 2022 and transmitted to the BAC, after which the BAC was able to come to a conclusion with respect to the environmental aspects associated to the proposed clinical trial.

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 did receive three reactions from the public of which none were related to biosafety issues.

Summary of the scientific evaluation

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

The donor, recipient and parental organisms are adequately described in the dossier.

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

According to the Belgian classification and the Canadian Pathogen Safety Data Sheet, the Indiana Vesicular Stomatitis virus, the parental virus from which VSV-GP (BI 1831169) is derived, corresponds to a risk group 2 for human pathogens and a risk group 3 for animals. Humans can contract VSV through direct contact with infected animals or indirectly through the bite of an infected fly. VSV tropism and specificity is mediated by the VSV glycoprotein, which has been replaced by the LCMV glycoprotein in BI 1831169. Doing so, both neurotoxicity of the oncolytic virus and pathogenicity in livestock (e.g. pig model) have been abrogated as compared to the parental virus. Since the main transmission routes of LCMV to humans are urine, feces, saliva from mice, the risk of vector-borne transmission of BI 1831169 can be considered as negligible.

3. The conditions of the release

There are no clinical data with VSV-GP at this time. A non-clinical safety study has been performed to evaluate the safety and biodistribution of VSV-GP on healthy mice after a single intravenous and subcutaneous dose. No genomic material could be detected in blood, brain, heart, kidney, liver, and lung beyond 14 days after treatment, except in the spleen. Long-term persistence (D61 after injection) is observed in the spleen of mice dosed with VSV-GP (as measured by RT-qPCR assay),while no infectious material was detected by $TCID_{50}$ activity. Similar findings on persistence of viral RNA with no active replication were made for wt VSV (Simon *et al*., 2010).

Ian D Simon *et al*. Vesicular stomatitis virus genomic RNA persists in vivo in the absence of viral replication. J Virol. 2010 Apr; 84(7):3280-6

For this first in-human study, the virus shedding assessment will be performed on buccal swabs, nasal swabs, i.v./i.t. administration site swabs and urine samples, collected from all patients that have received BI 1831169. Although, shedding of genomic material from the feces of tumor-bearing mice treated with one single dose i.v. of i.t of VSV-GP was observed 24h post injection, feces samples have not been included for the shedding analysis in this study as tenacity studies have showed that $TCID_{50}$ titers for BI 1831169 in feces were below the quantitation limit after ≥ 3 hours at room temperature. Shedding samples will be collected at all visits until the end of treatment visit (26 days after last dose of IMP) at the hospital. Since it cannot be excluded that the shedding results will be negative at the End of Treatment visit (EOT), the notifier confirmed that extra shedding samples will be collected after the EOT visit if required. In this case, the protocol will be amended accordingly following BAC's request.

The oncolytic virus, VSV-GP will be administrated in 5 times on C1D1, C1D4, C2D1, C3D1 and C4D1. The notifier confirmed that the patients will be admitted overnight following cycle 1 day 1 and day 4 as well as cycle 2 day 1. Patients will be required to stay overnight following their C3D1 or C4D1 treatment only if results from previous cycle are positive and over a certain threshold (≥ 2×10^5 copies).

Several instructions (such as bringing back to hospital any potentially contaminated material (e.g. plasters), reduction of close contact with vulnerable people, avoiding contact with livestock for 10 days following treatment administration…) will also be given to patients to help prevent dissemination of the viral vector once they are at home. The notifier agreed to implement these instructions by adding the prohibition of sexual intercourse, the collection of gloves that were used to change the dressing and single-use tissue used when coughing or sneezing and by adding rodents in the list of animals that should be avoided since rodents also correspond to a wt virus host according to the Pathogen Safety Data Sheets: Infectious Substances –Vesicular stomatitis virus (VSV). These instructions will have to be followed for 10 days after each administration of BI 1821169 by the patients.
The BAC also advised to consider restriction on blood/cells/tissues/organs donation for 6 weeks following last injection of BI 1831169 as part of the exclusions criteria for the proposed study.
The notifier was asked to further specify the properties of the bandage and the modalities of use to prevent fluid from being exposed to others. Upon BAC's request, the notifier adapted the recommendations to be given to the patient. The airtight and watertight bandage should be sealed on all four sides on the injection site immediately after injection and should be changed at least once every 48 hours until lesions have completely disappeared.

All these instructions for the patients with respect to good hygiene practices have been detailed in a short, readable format document that will be provided to each patient.

4. The risks for the environment or human health

VSV-GP is a GM, replication-competent recombinant Vesicular Stomatitis Virus (VSV) carrying the glycoprotein (GP) of Lymphocytic Choriomeningitis Virus (LCMV). Both neurotoxicity of the oncolytic virus and pathogenicity in livestock (e.g. pig model) have been abrogated as compared to the wild type parental VSV strain.

Since wild type VSV replicates within the cytoplasm of infected cells without intermediate DNA, there is negligible risk for integration in the genome of the host cell. Furthermore, since wild type VSV has a single stranded genome and always forms nucleocapsid structure, recombination with host cell

sequences is highly unlikely. Homologous recombination with VSV strains is not believed to occur to any significant extent in part because BI 1831169 does not cause long-lasting or chronic infections in the host and thus, probability of co-infection is low.

Reversion of BI 1831169 back to a wild type VSV is not expected as the whole VSV-G sequence has been removed in the current BI 1831169 genome. Reversion back to a wild type LCMV is not possible as only the GP sequence of LCMV is present in BI 1831169.

In the case of transfer of vector to an unintended immune-competent human recipient, the risks are expected to be considerably reduced as compared to any potential risk for the participant, since the 'dose' that may conceivably be transferred (from e.g. aerosol, splashing or fomites) will be orders of magnitude lower than that received by patients. Furthermore, both innate and adaptive immune responses will contribute to rapidly contain viral infection.

Upon BAC's request, the notifier provided a 2-4 pages technical sheet 'Instructions for study site personnel' including all relevant handling instructions, such as those to minimize aerosol formation, detailed instructions in case of accidental spill or breakage of a vial containing the GMO and waste management (elimination or inactivation of unused stocks, left-overs). The notifier also provided more details on the instructions for the in-house transportation of the vector on site, on the instructions in the case of self-accidental injection of the medical personnel, the exact compound and/or the precise percentage or concentration in the final solution for each disinfectant.
BAC also specified that a ready-to-use spill kit must be present in or near the areas where the GMO is handled and administered and that a FFP2 masker must be used during the preparation and administration of the viral vector.

The notifier confirmed that the intra-tumoral administration of BI 1831169 by the physician investigator will be performed in a hospital room that should meet BSL-2 area criteria.

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

Given the assessment of the likelihood of further propagation of BI 1831169, the BAC supports the view that, in terms of risk for the environment or human health, the proposed measures as described in the revised documents are proportionate and adequate in the context of the intended trial.

Conclusion

Based on the scientific assessment of the notification made by the Belgian expert, the Biosafety Advisory Council concludes that it is unlikely that BI 1831169 developed as an oncolytic virotherapy will have adverse effects on human health or on the environment in the context of the intended clinical trial provided that all the foreseen safety measures are followed as described in the following new or updated documents (and for some still to be adapted in accordance with the conditions stipulated below):

- Part 1A_VSV-GP-CAF - *to be updated in accordance with condition 1 here below*
- Part 1B_Confidential_Annex_CAF (version 1.2, 17 May 2022)
- Technical Sheet for Site Staff (version 1.0, 07 Dec 2021)
- 1456-0001 Study Participant Summary Sheet (version 12, May 2022)

- ICF-Main-M_03_BEL01 (version 03, 16 Nov 2021) and Protocol (version 2.0, 09 Nov 2021) – *to be updated in accordance with condition 2 here below*

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

1- According to the Belgian classification and the Canadian Pathogen Safety Data Sheet, the Indiana Vesicular Stomatitis virus corresponds to a risk group 2 for human pathogens. It is therefore not correct to claim that "*VSV is not considered a human pathogen*". The notifier is requested to correct this sentence by clearly indicating that Indiana VSV is classified as Risk Group 2 human pathogens in the following documents:
   - o ICF_EN (page 7/59),
   - o ICF_FR (page 7/65),
   - o ICF_NL (page 7/69),
   - o SNIF (pages 2/19 and 5/19)
   - o CAF (pages 7/41, 9/41 and 37/41)

2- The protocol and the Informed Consent Form will be updated and submitted to the Biosafety Advisory Council prior to initiating the study in Belgium with the following changes:
   - o Rodents must be added in the list of animals to avoid from C1D1 to the end of treatment visit (Part 1 patients) or C5D1 (Part 2 patients)
   - o An exclusion criteria for restriction on blood/cells/tissues/organs donation for 6 weeks following last injection of BI 1831169 must be added in the list of criteria
   - o The recommendation to abstain from sexual intercourse for the 10 days following treatment due to the possibility of shedding must be added in the list of instructions for the patient
   - o It should also be clearly indicated in the protocol that Indiana VSV is classified as Risk Group 2 human pathogen

3- The notifier and the investigators must strictly apply the clinical trial protocol and all the safety instructions as described in the dossier and the updated and new documents listed here above.

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

5- The notifier is responsible to verify that the 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.

6- At the latest 15 days after the start of the trial, the notifier should provide, along with the delivery of the control sample, a detailed protocol for the method of conservation and analysis of the control sample.

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

8- At the latest six months after the last visit of the last patient included in the trial, the notifier must send to the competent authority at the attention of the Biosafety Advisory Council a report with details concerning the biosafety aspects of the project. This report shall at least contain:
    - The total number of patients included in the trial in Belgium;
    - A report of the shedding data obtained from the clinical trial (monitoring of viral vector excretion/secretion in buccal swabs, nasal swabs, i.v./i.t. administration site swabs and urine samples after each injections at C1D1, C1D2, C1D4, C1D5, C1D8, C1D15, C2D1, C2D2, C2D8, C3D1, C3D8, C4D1, C4D8, EOT)
    - 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 BI 1831169.

Prof. Dr. ir. Geert Angenon
President of the Belgian Biosafety Advisory Council

Annex I: Compilation of comments of experts in charge of evaluating the dossier B/BE/21/BVW7 (ref. SC/1510/BAC/2022_0171 and SC/1510/BAC/2022_0516)

Adviesraad voor Bioveiligheid
Conseil consultatif de Biosécurité

Compilation of comments of experts in charge of evaluating the dossier B/BE/21/BVW7 And comments submitted to the notifier

10 February 2022
Ref. SC/1510/BAC/2022_0171

Mandate for the Group of Experts: Mandate of the Biosafety Advisory Council (BAC) of 09 december 2021.
Coordinator: Karen Willard-Gallo (Jules Bordet Institute, ULB)
Experts: Nicolas van Larebeke-Arschodt (UGent, VUB), Anton Roebroek (KULeuven), Willy Zorzi (ULiège), Aline Baldo (SBB)
SBB: Sheela Onnockx

INTRODUCTION

Dossier **B/BE/21/BVW7** concerns a notification from SCS Boehringer Ingelheim 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 06 January 2022 and concerns a clinical trial entitled "*Phase I open-label, dose escalation trial of BI 1831169 monotherapy and in combination with ezabenlimab in patients with advanced or metastatic solid tumors".*
The trial will involve the use of a genetically modified viral vaccine, VSV-GP, which is a recombinant vesicular stomatitis virus carrying the glycoprotein (GP) of the visceral non-neutropic WE-HPI strain of the LCMV virus. Patients will receive BI 1831169 intratumoral injection (Arm A), intravenous infusion (Arm B) or combined i.t. and i.v. (Arm C) alone or in combination with ezabenlimab (Arms D, E and F).

♦ 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/questions received from the experts

Remark: The comments below have served as basis for a list of questions that the Competent authority forwarded on 07-02-2022 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.

2. INFORMATION RELATED TO THE INVESTIGATIONAL MEDICINAL PRODUCT

A.1. Virus from which the clinical vector was derived (parental virus)

(e.g. information on parental virus; phenotypic and genetic markers; host range, zoonotic potential and replication properties of the parental virus ….)

Comment 1

Summary Notification p4 I wonder what is precisely meant by
(c) Is it frequently used in the country where the notification is made?
Yes (.) No (X)
(d) Is it frequently kept in the country where the notification is made?
Yes (.) No (X)

SBB Comment:

These questions reported in section B of the SNIF provide information on the geographical distribution of the organism, the frequency of use and the prevalence of the organism in the country where the clinical trial will be performed. As mentioned by the notifier, wt VSV is reported to exist exclusively in the western hemisphere. It is maintained in stable ecologic niches in Central and South America and Mexico and emerges from tropical areas to cause sporadic epidemics in cooler climates during the summer months. Europe is not an endemic area for VSV.

Comment 2

Has evaluated this item and has no questions/comments.

Comment 3

Has evaluated this item and has no questions/comments.

Comment 4

The notifiant considers in the dossier that VSV is not consider a human pathogen (p7/39). VSV is considered as a human pathogen (see Pathogen safety data sheet – infectious substances; Belgian classification: Vesicular Stomatitis Indiana virus risk group 2 for human and risk group 3 for animals).

SBB Comment:

Pathogen safety data sheet can be found on the Belgian Safety Server in the Revised lists of pathogens and their corresponding class of biological risk (https://www.biosafety.be/content/tools-belgian-classification-micro-organisms-based-their-biological-risks; https://www.biosafety.be/sites/default/files/h_a_virus.pdf)

Coordinator Comment:

Yes, she is right and this could be corrected

A.2. Pathogenicity

(e.g. pathogenic properties, available treatment methods, attenuation and biological restrictions of the parental virus ….)

Comment 1

The wild type VSV virus should be considered a potential human pathogen, but only resulting in mild illness. However, no large studies have been performed to address pathogenic properties of the parental virus in vulnerable groups such as immunosuppressed individuals, pregnant women and small children

SBB Comment:

According to the VSV Pathogen Safety Data Sheet of Public Health Agency of Canada (http://www.phac-aspc.gc.ca/lab-bio/res/psds-ftss/stomatit-eng.php), most human infections with Indiana and New Jersey VSV serotypes appear to be subclinical. In patients that show clinical manifestations, the initial symptom is high fever that is often biphasic. Subsequent symptoms are "flu-like" including severe malaise, headaches, myalgia, arthralgia, retrosternal pain, eye aches, and nausea. As reported in the inclusion and exclusion criteria, vulnerable groups such as primary immunosuppressed individuals, pregnant women and small children are excluded from this clinical trial. Furthermore, instructions will be given to patient to avoid close contact with young children, pregnant women, immunocompromised people and livestock (e.g., pigs, cows, horses, etc.) and when unavoidable, a surgical grade mask should be worn when within touching distance.
However, the notifier could be requested to evaluate the possible consequences of horizontal transfer of the IMP to immuno-compromised people, pregnant women and children. Is it conceivable that such people could present unanticipated shedding pattern following accidental infection with VSV-GP.

Coordinator Comment:

It is important to underline the need for these instructions.
Regarding the evaluation of the possible consequences of horizontal transfer: Not sure that this is necessary and is out of scope for their study but it is important that they control and follow up that contact with these vulnerable groups is avoided.

Comment 2

Has evaluated this item and has no questions/comments.

Comment 3

Has evaluated this item and has no questions/comments.

Comment 4

Given that no large studies have been performed to address pathogenic properties of parental virus in vulnerable groups such as immunosuppressed individuals, pregnant women and small children, particular attention should be paid to their protection.

SBB Comment:

See SBB comment above under section A2, comment 1 of this document

Coordinator Comment:

This statement made a little stronger should suffice:
Given that no large studies have been performed to address pathogenic properties of parental virus in vulnerable groups such as immunosuppressed individuals, pregnant women and small children, it is CRITICAL that clear instructions are provided to health care workers administering the treatment on the need to emphasize to the patient the importance of avoiding contact with these groups outside of the hospital setting.

Additional SBB comment:

SNIF, section E.1.d, p11/19: replacing the glycoprotein G of the VSV by the GP of the LCMV abrogates neurotoxicity (Muik et al, 2014, Cancer Res). These results have been obtained in mice and even if VSV-GP vector seems to be safe in mice, this hasn't been shown in humans. Therefore, the notifier could be requested to indicate in the SNIF that the safety profile of the VSV-GP vector has currently only been studied in mice with no available human data. Same comment for the CAF 14/39, section 2.15

A.3. Ability to colonise

(e.g. transmission routes, survival outside the host….)

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Has evaluated this item and has no questions/comments.

Comment 3

Has evaluated this item and has no questions/comments.

Comment 4

Humans can contract VSV through direct contact with infected animals, or indirectly through the bite of an infected fly. This mode of transmission in humans is not considered but should be by the notifiant.

SBB Comment:

According to section A.3 of the CAF (p10/39), VSV is an arthropod-borne virus, with transmission between natural hosts occurring through the bite of sand flies.

B. Genetic modification and manufacturing of the clinical vector

(e.g. manufacturing process of the vector; characteristics of the cell lines used for production, information on replicating –competent virus…)

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Has evaluated this item and has no questions/comments.

Comment 3

The quality of the figures in the Confidential Annex – Common application form is insufficient to allow reading of details and is consequently in fact unacceptable for a document of this type. Fortunately, the description of largely the same plasmids in a Confidential Annex – Common application form of another dossier could be used to circumvent this problem with respect to the quality of the figures. This is, however, only possible, if this other confidential document is available to an evaluator.

SBB Comment:

The quality of the figures in the Confidential Annex – Common application form is insufficient to allow reading of details and is consequently in fact unacceptable for a document of this type. The notifier could indeed be requested to provide an updated document with readable figures.

Coordinator Comment:
High resolution images should be provided throughout the dossier.

Comment 4
Has evaluated this item and has no questions/comments.

C. Clinical vector

2.13. - 2.16 . Map of the clinical vector and molecular characteristics, coding genes and regulatory sequences, biologic profile of the clinical vector versus parental virus

Comment 1
Has evaluated this item and has no questions/comments.

Comment 2
Has evaluated this item and has no questions/comments.

Comment 3
Same comment as for B

Comment 4
The possible transmission route of VSV-GP remains unclear but considering the transmission routes for both parental viruses, it might occur via direct contact or contact to excretions or body fluids. Arthropod vector transmission should also be considered in the environmental risk assessment.

2.17. Potential for recombination

Comment 1
Document B_BE_21_BVW7_Part 1A_VSV-GP-CAF: p13: "The biology of VSV-GP in general allows for complementation by alternative viral surface proteins" Does this mean that the virus might incorporate other proteins that might change its interactions with potential target cell surfaces and thus broaden its spectrum of infectable cells?

SBB Comment:
The approach in developing VSV vectors consists in deleting (part of) the sequence encoding for the natural occurring envelope protein responsible for attachment to cells, VSV G, and to replace it with sequences encoding one or more heterologous envelope proteins able to reconstitute the attachment, fusion and budding function. For virions expressing surface-exposed heterologous proteins playing a role in cell attachment, the collection of specific data on tropism, biodistribution and shedding properties becomes key to a good understanding of their in vivo behaviour (Baldo et al, 2021).

Document B_BE_21_BVW7_Part 1A_VSV-GP-CAF: p13 "Recombination events with host cell mRNAs have been observed but are controversially discussed among experts with the VSV polymerase (L)

described to not allow recombination (R21-2989 Lai, 1992)." We cannot assume that it is proven that recombination with cellular RNA's is impossible.

SBB Comment:
Although, the frequency of recombination among negative sense RNA viruses seems to be relatively low, Chare et al., 2003 reported patterns of sequence variation compatible with, but with no direct evidence for, recombination for 10 viruses including Vesicular Stomatitis virus, which suggests that it is indeed not possible to rule out recombination.

Coordinator Comment:
Important to make a comment on this.

Document B_BE_21_BVW7_Part 1A_VSV-GP-CAF: p15 "Besides the use of alternative cell receptors and the abrogation of neurotoxicity in VSV-GP, other viral properties like the VSV-mediated interferon sensitivity are considered preserved" Are there experimental data to back this up?

SBB Comment:
Wild type VSV is sensitive to type I IFN responses, and preferentially replicates in cancer cells. VSV-GP has been designed to be replication competent, and its intent is to infect, replicate in and kill interferon deficient cancer cells. According to Muik et al (Cancer Res, 2014), VSV-GP retained wt VSV's potent oncolytic activity in both syngeneic and xenogeneic orthotopic brain cancer models in mice.

Document B_BE_21_BVW7_Part 1A_VSV-GP-CAF:p16 "The absence of neuronal side effects in patients treated in clinical trials with VSV based oncolytic viruses (VSV-bIFN and Maraba virus) or vaccines (VSV-EBOV) and the fact that in mice VSV-GPs safety profile is superior (R21-2998 Wollmann et al., 2015) leads to the conclusion that there is only minimal risk even in vulnerable groups (such as cancer patients)".The Wollmann paper shows a clear difference, but also the LCMV chimeric VSV virus showed some neurologic toxicity. Furthermore, it is not because Thomsen et al. show that adaptive immune responses, especially CD4+ T cells play a role in the protection against encephalitis that this protection is total or sufficient

SBB Comment:
From the perspective of the environmental risk assessment, exposure of non-target individuals (e.g. accidental exposure of heath care professionals at clinical trial site; exposure of close contacts because of shedding) will be exposed to much lower amounts of the drug product compared to the clinical dose. The potential of generating some neurologic toxicity, is considered to be a patient safety related concern, which is addressed within the clinical assessment of the proposed trial and which goes beyond the scope of the environmental risk assessment or the biosafety assessment of the proposed trial.

Coordinator Comment:
Coordinator agreed with SBB comment

SUMMARY NOTIFICATION P15 point7: Do we effectively have experimental data which show that the coding RNA from the virus does never reach the nucleus and does not give rise to DNA sequences that can interact with the host DNA?

SBB Comment:
The replication of Rhabdoviruses including VSV exclusively occurs in the cytoplasm and does not include a DNA intermediate. From an environmental risk perspective, if inadvertent integration would

occur, it would potentially contribute to germline transmission. According to the EMA 'guideline on nonclinical testing for inadvertent germline transmission of gene transfer vectors', if viruses are considered non-integrating, because they lack the machinery to actively integrate their genome into the host chromosomes, and if biodistribution studies do not reveal vector distribution to gonads, germline transmission studies are not considered necessary. Ref : EMA. Guideline on nonclinical testing for inadvertent germline transmission of gene transfer vectors 2006 28 February 2019. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-non-clinical-testing-inadvertent-germline-transmission-gene-transfer-vectors_en.pdf.

Coordinator Comment:
Coordinator agreed with SBB comment

SUMMARY NOTIFICATION P15 point7 b: : I expect that the viral RNA is liberated from nucleoproteins during the replication of the virus and could then interact with other RNA's
SUMMARY NOTIFICATION p 15& 16: I do not understand that recombination could only occur between VSV-GP viruses. I think that it could also occur with other viruses, and particularly with other VSV or LCMV viruses.

SBB Comment:
Since Europe is not an endemic area for wt VSV, the probability of simultaneous co-infection of a cell with VSV-GP and wt VSV is estimated to be negligible. However, since it not possible to rule out the presence of wt VSV at time of the clinical trial, the applicant could be suggested to further nuance the statement concerning the possibility of recombination between VSV-GP and wt VSV viruses or VSV-GP and LCMV viruses.

Coordinator Comment:
The coordinator is not really sure this is necessary…

Comment 2
Has evaluated this item and has no questions/comments.

Comment 3
Has evaluated this item and has no questions/comments.

Comment 4
Has evaluated this item and has no questions/comments.

2.18. Biodistribution and shedding

Comment 1
Document B_BE_21_BVW7_Part 1A_VSV-GP-CAF P17 "Genomic material was present in the spleen at levels above lower limit of quantification (LLOQ) on day 61 in 7 out of 10 mice." I suppose that this indicates that viral proliferation occurred in splenic tissues as it is unlikely that RNA remains present over such a long period

SBB Comment:
Proposed wording for question :
The notifier mentioned in section Biodistribution in healthy mice, on p18/40 of the VSV-GP-CAF, that genomic material was present in the spleen at levels above the lower limit of quantification (LLOQ)

on day 61 in 7/10 mice. The notifier is requested to clarify whether viral proliferation occurred in splenic tissues since it seems unlikely that RNA remains present over such a long period.

Coordinator Comment:
The spleen is a filter organ so it could come from elsewhere in the body and enter through the blood. Probably good to ask them to clarify.

Comment 2
Has evaluated this item and has no questions/comments.

Comment 3
No data on shedding of the vector in humans are known yet. Data on shedding are only available for animals.
The natural hosts of the parental virus VSV include primarily lifestock. The application of VSV-GP (BI 1831169) was apathogenic in pigs (i.e., no vesicular lesions were observed on the snouts of the VSV-GP infected animals) and no shedding was detected, except for minimal amount of virus at the nose swab, the administration site.
Furthermore, mice, rabbits and dogs were challenged by injection with VSV-GP. The results of the studies in these animals suggest, that shedding (analyses of injection-site swabs, buco-nasal swabs, urine, and faeces) is not really an issue, since no shedding of infectious material was detected (above LLOQ) except for tumor-injection site swabs in mice. In the FIH clinical trial, shedding of VSV-GP (BI 1831169) will be investigated further for humans.

SBB Comment:
BI 1831169 is administered in 21-day treatment cycles. Four cycles of therapy are planned. In the first cycle, BI 1831169 will be administered on Day 1 and Day 4. In each of the following cycles BI 1831169 will be administered on Day 1 only. Buccal, nasal, tumour site (superficial lesions only), and i.v. site swabs and urine sample will be collected and processed. All patients will be admitted overnight following cycle 1 day 1 and day 4 as well as cycle 2 day 1 to assess for any AEs and collection of samples. For cycles 3 and 4, if the results from previous cycle are positive and over a certain threshold (≥ 2 x105 copies), the patient will be required to stay overnight following their C3D1 or C4D1 treatment and the shedding sampling schedule should be performed in full as per cycle 2 day 1 and 2.

Coordinator Comment:
Maybe we can add a positive sentence about the importance of doing these analyses?

Comment 4
The virus shedding will be assessed in buccal, nasal and administration site swabs and urine. Could the applicant provide the timelines for the collection of samples? Are these samples collected in the hospitals or at home?

SBB Comment:
According to the flow chart Part 1 and Part 2 of the protocol, shedding samples will be collected at C1D1, C1D2, C1D4, C1D5, C1D8, C1D15, C2D1, C2D2, C2D8, C3D1, C3D8, C4D1, C4D1 and C4D26.

Additional SBB comment:
Patients will be admitted overnight following cycle 1 day 1 and day 4 as well as cycle 2 day 1. For cycles 3 and 4, the patient will be required to stay overnight following their C3D1 or C4D1 treatment only if results from previous cycle are positive and over a certain threshold (≥ 2 x10^5 copies). Since shedding properties of VSV-GP in humans are currently lacking, the notifier could be requested to justify the choice of not keeping patient automatically overnight at the hospital at cycles 3 and 4.

Coordinator Comment:
Yes this is an important comment.

3. INFORMATION RELATED TO THE CLINICAL TRIAL

3.3. Storage of the clinical vector at the clinical site

(e.g. storage location, conditions of storage, …)

Comment 1
Document B_BE_21_BVW7_Part 1A_VSV-GP-CAF P20 There seems to be a contradiction or a confusion in the number of patients involved: 117 according to Document B_BE_21_BVW7_Part 1A_VSV-GP-CAF and 4 according to document " 2020-003902-30_VSV_GP_SNIFF_VSV-GP_BE_Brussels_2021118". Would the total number of patients world-wide amount to 117 and the number in Belgium to 4?

SBB Comment:
In total approximately 117 subjects will take part in the study that has been submitted in the EU to Austria, Belgium and Germany. Approximately 4 patients are expected to be enrolled in Belgium.

Comment 2
Has evaluated this item and has no questions/comments.

Comment 3
Has evaluated this item and has no questions/comments.

Comment 4
Storage access should be restricted to the people involved in the clinical trial.

SBB Comment:
According to section 3.3.1, storage of the clinical vector at the Cliniques Universitaire Saint-Luc, "the concentrate of the clinical vector will be stored in sealed containers that are labelled with descriptions of the GMO, and it will be placed in a properly controlled freezer within the hospital pharmacy. Access is only granted to authorized pharmacists."

Coordinator Comment:
This is standard protocol.

Additional SBB comment:
According to SNIF p14, CAF p32/39 and CAF p36/39, one specific measure proposed to minimize the probability of virus transfer to livestock animals and the environment will be: "Isolation of the patient *during after* the treatment, surgical grade mask wearing for the 10 following days to each treatment". It is not clear whether the patient will be isolated during and/or after treatment? Will the patient be isolated for 10 days after each administration of the treatment? How stringent will this isolation be? Isolation

within the house (separate bedroom,…) or isolation from other people outside the house? The notifier could be requested to clarify this point in both documents.

Additional SBB comment:
In the SNIF, it is not clear for how long the patient should avoid contact with livestock:
In SNIF, section F.4.c, p14, it is stated that : *Providing the clear instructions to the subject of treatment to avoid the contact with livestock animals (e.g. pigs, cows, horses, etc.) during 10 days after the administration*, while in the SNIF, section G.3, p15, it is mentioned that : patients are given biosafety advice to follow in the two weeks after treatment, such as avoiding contact with livestock and using appropriate waste disposal measures, e.g. for plasters that were in direct contact with the VSV-GP injection site.
The notifier could be requested to clarify in the document the exact period when the patient should avoid contact with livestock and whether these instructions should be followed after each administration of the viral vector.

Additional SBB comment:
The following question has been sent to the notifier for the dossier B/BE/21/BVW4 and could also be sent for this dossier too:
The notifier is requested to clarify why patients are still allowed to have protected intercourse when, on the other hand, for safety reasons, they are recommended to avoid common usage of unwashed cutlery, crockery, and drinking vessels, to store any soiled clothing separately from any other people living in the same accommodation and to use a separate toilet when possible and to add bleach or equivalent products to the toilet after each use. In order to be consistent with the recommendations provided to the patient, the notifier is requested to ask the patient to abstain from sexual intercourse until 3 negative, consecutive results are obtained from the RT-PCR analysis of viral shedding samples.

Additional SBB comment:
The following question has been sent to the notifier for the dossier B/BE/21/BVW4 and could also be sent for this dossier too:
CAF, p19/39: The notifier mentions that "VSV-IFNβ-NIS oncolytic virus was demonstrated recently to be safe for caregivers, with no viral shedding, even with increased infusion duration (Merchan et al., 2020)". However, the document 'Merchan_2020' provided as a reference is only an abstract with a table, which is not very informative for the shedding data collected. Since exposure of the viral vector to study nurses or surgeons during surgery cannot be totally excluded, more detailed information, including the nature of the clinical samples taken, the time points when samples are and the detection limit are necessary to evaluate the information in this table. The notifier is asked to provide further information that would permit proper assessment of these data in the table?

3.4. Logistics for on-site transportation of the clinical vector

(information on logistics of in-house transportation, characteristics of the container, disinfection procedures, labelling of the containers, ...)

Comment 1
Has evaluated this item and has no questions/comments.

Comment 2
Has evaluated this item and has no questions/comments.

Comment 3

The on-site transportation of the GMO/clinical vector after dose-preparation in the hospital pharmacy to the hospital rooms where the administration to the patient will take place, is only very briefly described ("carried in a sealed state" as written on page 21/39 of the CAF). The precise characteristics of the transport carrier used should be described: unbreakable and unleakable (preferably with internal absorbent material) even in case of an accident during transport.

SBB Comment:

Aside from the brief description of on-site transportation of the clinical vector after dose-preparation in the hospital, nothing is mentioned on the precautions that should be taken to protect the syringe and the needle during transport and ensure protection of the staff and environment against accidental exposure (prick or spill). The notifier could be requested to provide detailed instructions for transporting the prepared medicinal product from the pharmacy to the hospital room, including the type of suitable hermetic transportation container containing absorbent paper towels, labelling of the container, etc… and how the syringe and needle be protected during transportation.. Furthermore, CAF, section 3.6.a refers to a document "Instructions for Preparation and Administration of BI 1831169". However, this document has not been provided. The notifier could be requested to provide this document.

Comment 4

The internal transport of the vials containing the IMP should be performed in an hermetic transport box containing absorbent paper towels.

SBB Comment:

See SBB comment above under section 3.4, comment 3 of this document

3.5. Reconstitution, finished medicinal product and administration to the patients

(e.g. mode of administration, information on dosing and administration schedule, information on concomitant medication,…)

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Has evaluated this item and has no questions/comments.

Comment 3

Has evaluated this item and has no questions/comments.

Comment 4

FFP2 mask should be used for i.t administration of the IMP.

SBB Comment:

According to the VSV Pathogen Safety Data Sheet of Public Health Agency of Canada (http://www.phac-aspc.gc.ca/lab-bio/res/psds-ftss/stomatit-eng.php), mode of transmission of VSV corresponds to bite of an infected sand fly; by direct contact with abrasions on the skin; by contact with infected domestic animals; or by inhaling aerosols via the nasopharyngeal route. Since VSV transmission can occur through inhaling of aerosols, the notifier could be requested to recommend that an FFP2 mask be work during the preparation and administration of the IMP.

3.6. Measures to prevent dissemination into the environment

(e.g. control measures, PPE, decontamination/cleaning measures after administration or in the case of accidental spilling, waste treatment, recommendation given to clinical trial subjects, …)

Comment 1

Document B_BE_21_BVW7_Part 1A_VSV-GP-CAF P25 "Potential environmental risk is addressed via exclusion of the patients that are not expected to comply with the protocol requirements": The proposed phase1 first in humans release of the VSV-GP virus caries a risk that is orders of magnitude higher than the risk associated with releases of other genetically modified organisms that are not replication competent or do not carry the pathogenic cytotoxic potency (on which the anti-cancer effect rests) associated with the VSV-GP virus. This does not mean that the phase1 trial with VSV-GP virus should be forbidden, but it indicates that extremely efficient safety measures should be taken to prevent the spread of VSV-GP before more knowledge on the effect of the release of the virus is available. In particular the participating patients should be fully informed of these risks and in the selection of these patients their capacity to deal with this knowledge and problem should be taken into account

SBB Comment:

In order for the patients to adhere to and practice good hygiene, it is very important to explain why measures need to be followed and identify to them the likely sources of contaminated material. The applicant is requested to prepare a small take home summary (preferably a one-page, plasticized document) to ensure that this information in laymen's language is readily available for patient to consult at any time.

Document B_BE_21_BVW7_Part 1A_VSV-GP-CAF P26 ffp2 masks should be worn instead of surgical masks

SBB Comment:

See SBB comment above under section 3.5, comment 4 of this document

SUMMARY NOTIFICATION p13 "Proximity to internationally recognised biotopes or protected areas (including drinking water reservoirs), which could be affected:
Not applicable as administration will only occur in the clinic."
This answer is not sufficient. Participating patients should be instructed to avoid certain areas and certain contacts.

SBB Comment:

Patients will receive some instructions when going back home in order to avoid potential virus transmission to other people or the environment. Included in the instructions, patients should be asked to avoid close contact with young children, pregnant women, immunocompromised people and livestock (e.g., pigs, cows, horses, etc.). When unavoidable, a surgical grade mask should be worn when within 1.5 meters. Patients who received an intratumoral injection in the oropharyngeal sphere should wear a surgical grade mask as much as possible, especially when in within 1.5 meters of other people. Whenever possible, the patient should use a separate toilet.

SUMMARY NOTIFICATION p14: sufficient aeration of the rooms in which the patient is taken care off.
SUMMARY NOTIFICATION P15 point 6:It cannot be excluded that some mammalian animals might be infected

SBB Comment:

Mammalian animals such as horses, cattle, pigs, mules and rodents are known host ranges of the wt VSV. Due to the mild, self-limiting nature of the disease and unlikely international spread through trade of animals, VSV has been de-listed by the World Organization for Animal Health (OIE) as a reportable animal disease (http://www.oie.int/en/animal-health-in-the-world/oie-listed-diseases-2019/).

Comment 2

In the B_BE_21_BVW7_Part 1A_VSV-GP-CAF document concerning « COMMON APPLICATION FORM FOR VIRAL VECTORS CONTAINED IN INVESTIGATIONAL MEDICINAL PRODUCTS FOR HUMAN USE »

p23. c) Decontamination/cleaning measures after administration or in the case of accidental spilling (i.e. decontamination /cleaning measures of potentially contaminated materials, surfaces and areas). In addition, the disinfection procedures applied should be justified by providing evidence that the chosen method is sufficiently active against the clinical vector.

Handling of spills: Inform and warn colleagues in direct proximity. Allow aerosols to settle and, wearing protective clothing, gently cover spill with paper towels and apply appropriate disinfectant, starting at the perimeter and working towards the center. Allow sufficient contact time before cleaning up (30 min).

Comment : Please describe more clearly the procedure in the case of accidental spilling :
- which kind of appropriate disinfectant for which kind of decontaminated surface to treat : soil, bench, table… and the appropriate contact time for each disinfectant.
- what about the presence of ready-to-use spill kit in or near the rooms used for the handling of the GMO and for the administration of treatment to the patient.

SBB Comment:

The notifier could be requested to clearly describe the procedure to be followed in case of accidental spill. According to section 3.6.c of the CAF (p24/40), appropriate disinfectant will be used to clean up accidental spill. The notifier needs to identify the best disinfectant for each type of contaminated surface or solution, the incubation time for full disinfection and any precautions to be taken.
The notifier should also indicate that a ready-to-use spill kit must be present in or near the areas where the GMO is handled and administered. This spill kit should contain the appropriate disinfectant(s), personal protective equipment (PPE, i.e. gloves, safety glasses, laboratory coat, mask), tongs or forceps for clearing broken vials, absorbent paper towels, biohazard waste bags, etc.

p24. e) Waste treatment (including also –where applicable- decontamination and disposal of potentially contaminated waste that accumulates outside the clinical trial site). Where applicable, identify also the company responsible for waste management.

-Disposable material used is always eliminated in type 2 biological waste container that are sealed on site and incinerated off site (SUEZ Belgium).
Comment : Please change type 2 by B2 (following the Belgian waste regulation).

SBB Comment:

This comment could be added in the Typos and other errors/omissions section.

Coordinator Comment:
Yes

Comment 3
In the CAF, section 3.6.c (p23/39), the applicant states that BI 1831169 is susceptible to all disinfectants for enveloped viruses and is inactivated by 1% cresylic acid, phenolics, chlorinated phenol, 2.5% phenol, 0.4% HCl, 2% sodium orthophenylphenate 14, and sodium hypochlorite. Physical inactivation: BI 1831169 is inactivated by heating (60°C, 30min). BI 1831169 survives temporarily on contaminated surfaces.
The notifier is requested to mention in the text and, surely, in the "Technical-Sheet-For-Site-Staff" the exact compound (phenolics) and/or the precise percentage or concentration in the final solution (phenolics, chlorinated phenol, sodium hypochlorite) for each disinfectant.

SBB Comment:
Same question was sent to the notifier for dossier B/BE/21/BVW4 where the investigational medicinal product is a recombinant vesicular stomatitis virus carrying the glycoprotein (GP) of the LCMV virus and a gene coding for the multi-antigenic domain (Mad).

In the CAF, section 3.6.d (p24/39), special instructions should be mentioned about elimination or inactivation of unused stocks, left-overs resulting from the dose-preparations itself as well as the prepared dose, because these solutions contain the highest amounts of virus. In its present form, this section is mainly focused on patient samples and material.

SBB Comment:
Agrees with expert's comment

CAF, section 3.6.g (p25/39 and 26/39):
In order for patients to adhere to and practice good hygiene, it is important to explain why measures are taken, what are the likely sources of contaminated material and how to dispose of potentially contaminated material. The notifier could provide a small take home summary (preferably one-page, plasticized document) to insure, that the patients can easily consult the information in an understandable format whenever needed (in the patient's native language).

SBB Comment:
Same question was sent to the notifier for dossier B/BE/21/BVW4

Coordinator Comment:
Can't hurt to repeat this.

The notifier should be asked to explain why the measures to prevent dissemination by the patient into the environment are only applicable during the first 10 days following each treatment with the vector. Should the results of the analyses of shedding by the patients not be guiding for the time period to apply the recommendations?

SBB Comment:
Agrees with expert's comment. Since this study corresponds to a first-in-human study, no previous data on VSV-GP viral vector shedding is available. Although non-clinical data indicate that shedding of infectious VSV-GP particles is expected to be negligible, we cannot exclude that VSV-based viral vaccine may be present in biological fluids shed by the human subjects, particularly in patients who may be immunocompromised. Therefore, the notifier could be asked to adapt the oversight period from 10 days until the next administration or until the End of Treatment visit (to be performed around 26 days after last dose) if RT-PCR results for shedding on D8 are positive. Furthermore, since it

cannot be excluded that the shedding results will be negative at EOT visit, the notifier could be asked to elaborate on the impact of detecting undesirably high levels of shedding or prolonged shedding periods on protocol? Will there be extra shedding samples collected after the EOT visit? In these cases, will the protocol be amended accordingly?

The recommendations for 10 days following each treatment of BI 1831169 (p26/39) should mention besides lifestock also pets.

SBB Comment and Coordinator comment:

VSV infection occurs primarily in domesticated cattle, horses, swine, and rarely in llamas and humans. Infection of horses is particularly significant in the US (Rozo-Lopez et al., 2018, Insects). According to the Pathogen Safety Data Sheets: Infectious Substances – Vesicular stomatitis virus (VSV), rodents also correspond to the wt virus host range. Furthermore, serological surveys have shown that small grass-eating rodents, such as cotton rats and deer mice, might play a role in viral maintenance (Rozo-Lopez et al., 2018, Insects). Small pets, such as cats or dogs, have not been reported as hosts for the wt VSV. Since cotton rats could be a natural host of the wt VSV, the notifier is requested to adapt the recommendations given to the patient to prevent dissemination of the viral vector by adding rodents in the list of animals to avoid.

In the CAF section 3.6.h (p26/39) the applicant recommends to prohibit donation of cells and organs by the clinical trial subjects while on treatment and receiving BI 1831169. Since it is not evident to determine precisely when transfer of BI 1831169 is no longer a risk upon donation, it is advisable to prohibit donation by these (ex)cancer patients for good.

SBB Comment:

Vaccinated individuals with V920 (also known as rVSVΔG-ZEBOV-GP), a vaccine candidate for protection against EVD caused by Zaire Ebola virus (ZEBOV) must agree to not donate blood for 6 weeks following vaccination.

Donation of blood/cells/tissues/organs by a subject enrolled in the clinical trial conducted by AMAL Therapeutics (B/BE/21/BVW4) is not applicable since patients are at stage IV colorectal cancer.

Nothing has been mentioned regarding blood donation for subject enrolled in this clinical trial with BI 1831169.

In order to align recommendation for VSV-GP to the recommendation given for the rVSVΔG-ZEBOV-GP vaccination, The notifier could be requested to prohibit blood/cells/tissues/organs donations for 6 weeks following last injection of BI 1831169 to prohibit any possible transmission.

Comment 4

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.

SBB Comment:

This comment as been integrated into SBB comment above for comment 2 under section 3.6.

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 and mask should be decontaminated before disposal. The medical staff should report the incident to the responsible of the site.

SBB Comment:

In section 3.6.c of the CAF, the description of the procedures for the management of accidental spills could indeed be improved by adding the procedure as described here above.

Coordinator Comment:

Yes request that this be added to 3.6.c of the CAF

Infectious waste should always been incinerated even after inactivation on site.
Disposable material used is always eliminated in type 2 biological waste container that sealed on site and incinerated off site. There is a typo in the dossier: type B2 biological waste container.

SBB Comment:

Information regarding the incineration of the infectious waste has not been described in this Deliberate Release dossier. The notifier could be reminded that information regarding the incineration of all infectious waste must be described in detail in the Contained use dossier.

As mentioned for comment 2 in section 3.6 of this document, this typo error could be added in the Typos and other errors/omissions section.

Biohazard plastic bags should be provided at the clinical subjects with a clear procedure for the storage of dressing materials, equipment etc and bring back to the hospital.

SBB Comment:

The following question has been sent to the notifier for the dossier B/BE/21/BVW4 and could also be sent for this dossier too:

Biohazard plastic bags should be provided to the clinical trial subjects to dispose of waste (bandages, plasters, sanitary protections) by the patient at home. These bags are closed and brought back to the study site at the next visit for proper disposal by the hospital.

First, the notifier is requested to clarify in the documents what kind of bag or biohazard container should be used. Will these bags be provided to the patient? A clear procedure for the storage of dressing materials, equipment etc and bring back to the hospital should be described too.

Second, The following waste should also be disposed of in this bag:

- gloves that were used to change the dressing
- single-use tissue used when coughing or sneezing

Along with collecting biodistribution and shedding data, consideration should also be given to the replication competence and viremia levels. Given that VSV is a vector-borne virus, the likelihood that an insect may transmit the viral vector to another individual or animal upon a blood meal from an immunised person should be assessed.
However, if replication capacity and detected viremia levels are comparable to levels obtained with rVSVDG-ZEBOV-GP, it may provide a justification to waive the collection of data obtained in relevant insect lines as conducted.(cf Baldo et al., 2021 Vaccines – ERA of recombinant viral vector vaccines against SARS-CoV2)

SBB Comment:

The life cycle of VSV involves sandflies and rodent reservoirs. VSV-NJ and VSV-I can be transmitted between livestock by direct contact, likely including droplet spread and fomites, as well as mechanically by non-biting houseflies and face flies. Mechanical transmission by flies and animal-to-animal or animal-to-human transmission may occur.

Based on the vector-borne properties of wt-VSV, the notifier could be requested to discuss possible transmission by blood-feeding arthropods based on blood levels observed in animal studies. Is there

any replication data available of VSV-GP in arthropods (e.g. replication data in relevant arthropod cell cultures or live mosquitoes) that supports the minimal risk of transmission through insect vectors?

Additional SBB comment:

According to the technical sheet for site, "administration of BI 1831169 should be performed in a BSL-2 level treatment area, with i.t. administration being performed by a physician or radiological staff." However, according to section 4.1 of the CAF (p29/40), GMO injection will be performed in the hospital room which present a containment level of HR1. The notifier could be requested to clarify how the condition of a BSL-2 level area will be respected in the hospital room.

Coordinator Comment:

It is important to raise this discrepancy and to understand if it will be a physician/radiologist or a nurse who administers the investigational product.

Additional SBB comment:

Section 3.6.c of the CAF could be implemented by reporting that any spill incident must be reported to the intern prevention service of the hospital. The notifier could be requested to make sure such procedure has been put in place at UCL and to adapt the CAF accordingly.

Additional SBB comment:

The following question has been sent to the notifier for the dossier B/BE/21/BVW4 and could also be sent for this dossier too:

After injection, the injection site must be covered with an air- and watertight dressing for 2 days following BI 1831169 injection. The notifier is asked to indicate clearly in the CAF document the bandage characteristic sand modalities of use that insure fluid will not be exposed to others. The bandage should seal on all four sides, be properly applied without folds against the skin and be watertight. It should be applied to the injection site immediately after injection and should be worn, if necessary, until lesions have completely disappeared. It should be changed immediately if for any reason it no longer properly sealed and at least once every 48 hours. This information must be communicated via a small take home summary to the vaccinated patients since they or someone in their household is likely to change the bandage outside of a healthcare institution.

Additional SBB comment:

In order to help health care personnel, the notifier is asked to provide a 2-4 page 'instructions for study staff personal' provided as a plasticized document with the essentials for preparing and administering the IMP by personnel. This sheet should include all relevant handling instructions, detailed procedures to handling a spill including appropriate disinfectants, waste management and other risk management measures:

- Containment Level
    - o For IMP preparation
    - o For IMP administration
    - o Samples collection from the patient
    - o Samples storage
- Personal Protective Equipment (PPE)
    - o For the IMP preparation
    - o For the administration to the patients
    - o For the samples collection from the patient
- Management of inadvertent exposure of human to VSV-GP product

- Eye exposure from splash or aerosol
- Needlestick, sharps exposure or non-intact skin exposure
- Contact with skin and clothing

- Management of inadvertent exposure to blood, urine, vomit or other bodily fluids from patients in the initial period at the hospital
- Clean-up procedure
  - After IMP preparation (specify decontamination solution and minimum contact time)
  - In case of accidental spill or breakage (specify decontamination solution and minimum contact time)
- Waste Management
  - During IMP preparation
  - During IMP administration
  - During the 8h hospitalization of the patient
  - During samples collection from the patient

3.7. Sampling and further analyses of samples from study subjects

Comment 1

SUMMARY NOTIFICATION P17 Point 5: ""Duration of the monitoring" "The patient will be monitored for shedding of the virus from the day of the first treatment administration until the end of treatment visit." I suppose that what is meant here is that the patient will be monitored for shedding of the virus as long as he/she is in the hospital. I think however that some form of monitoring should be performed over the whole duration of the test procedure until May 2005, at least if indeed some shedding is observed for some patients during the hospitalization periods.

SBB Comment:

See SBB comment above under section 2.18, comment 3 of this document.

SUMMARY NOTIFICATION P17 Point 6: "Frequency of the monitoring " The patient will be monitored for shedding of virus at every visit. However as VSV-GP is replication competent a patient might shed virus over long periods. And also it is not clear at what point in time after an administration of VSV-GP the shedding of virus will be maximal.

SBB Comment:

In the clinical trial, buccal, nasal, tumour site (superficial lesions only), and i.v. site swabs and urine sample will be collected at C1D1, C1D2, C1D4, C1D5, C1D8, C1D15, C2D1, C2D2, C2D8, C3D1, C3D8, C4D1, C4D1 and C4D26.

Since no previous shedding analysis of the VSV-GP has been performed in humans yet, it is not possible to determine at the moment at what time point after administration, shedding of VSV-GP will be maximal.

VSV-GP viral shedding has been analysed in tumour-bearing mice, in healthy rabbits, in healthy dogs and in healthy pigs.

Coordinator Comment:

Monitoring of the shedding of the virus should be longer or more frequently if the patient remains positive

SUMMARY NOTIFICATION P18: "In case of self-accidental injection of medical personnel, the injection site will be disinfected, and personnel will be followed up in case of symptoms related to immune reaction against VSV-GP." The persons in question should be monitored for virus shedding

SBB Comment:

Instructions provided to the medical staff aim at minimizing the probability of health care personnel to be exposed to viral vector. However, self-accidental injection of medical personnel cannot be excluded. Monitoring to be put in place for this person should be proportionate to the risk. The notifier could be requested to provide any accidentally infected personnel with the same instructions and follow up given to the patients in this study.

Document B_BE_21_BVW7_Part 1A_VSV-GP-CAF P27 P 27 It is important that any samples that are taken to assess the possibility of shedding and contamination are taken, transported and kept under appropriate conditions to avoid false negatives.

SBB Comment:

As mentioned in the flow chart of the protocol, shedding samples for C1D1, C1D2, C2D1 and C2D2 must be shipped to the central lab within 48 hrs, all other shedding samples may be shipped in batch according to central lab. Details on sample collection, processing, handling, and shipment are provided in the Laboratory Manual.

Comment 2

Has evaluated this item and has no questions/comments.

Comment 3

According to the CAF (section 3.7.b; p27/39) and the protocol the shedding analysis is limited to buccal, nasal and i.v./i.t. administration swabs. The notifier should explain why feces is not included?

SBB Comment:

Buccal, nasal, tumor site (superficial lesions only), and i.v. site swabs and urine sample will be collected for shedding analysis.

Since shedding of genomic material from tumor-bearing mice treated with one single dose i.v. of i.t of VSV-GP via bucco-nasal swabs, urine, and feces was detectable in most samples collected at two hours (swabs only) and some samples 24 hours post-administration but was negative or < LLOQ at 72 hours, the notifier could be requested to explain why feces has not been included in the samples for shedding analysis.

Coordinator Comment:

This is more complicated to get patients to comply – and if the urine is positive the fecal samples will also likely be positive. You could ask…but

Comment 4

Along with collecting biodistribution and shedding data, consideration should also be given to the replication competence and viremia levels. Given that VSV is a vector-borne virus, the likelihood that an insect may transmit the viral vector to another individual or animal upon a blood meal from an immunised person should be assessed.

However, if replication capacity and detected viremia levels are comparable to levels obtained with rVSVDG-ZEBOV-GP, it may provide a justification to waive the collection of data obtained in relevant insect lines as conducted.(cf Baldo et al., 2021 Vaccines – ERA of recombinant viral vector vaccines against SARS-CoV2)

SBB Comment:

See SBB comment above under section 3.6, comment 4 of this document

3.8. Emergency responses plans

Comment 1
Has evaluated this item and has no questions/comments.

Comment 2
Has evaluated this item and has no questions/comments.

Comment 3
Has evaluated this item and has no questions/comments.

Comment 4
Has evaluated this item and has no questions/comments.

5. ENVIRONMENTAL RISK ASSESSMENT

Comment 1
Document B_BE_21_BVW7_Part 1A_VSV-GP-CAF P29 "Subjects presenting primary immune deficiency which could be at risk represent an extremely small population (500000 patients in the US have 1 of the 80 primary immune deficiencies, for a total population of more than 300 millions), and measures are in place in the protocol (see also Section 3.6) to prevent any unintended transmission."
Primary immune deficiency represents only a minority of all people suffering from defects in normal immune reactivity

SBB Comment:
Oncoselectivity of VSV is generally based on the lower type I IFN-associated antiviral potential of cancer cells compared to normal cells. Since immunocompromised persons could present deficiencies in a type I IFN response pathway and therefore not eliminate the virus as quickly as a healthy person, these patients might have an unanticipated shedding pattern following administration of VSV-GP. According to exclusion criterion 9, patients with history of primary immunodeficiency are not allowed in this clinical trial. Since primary immune deficiency represents only a minority of all people suffering from defects in normal immune reactivity, the notifier could be recommended to consider excluding any patients with a known immunodeficiency (beyond that acquired from their cancer treatment) from this VSV-GP study. The notifier could be requested to either adapt the protocol accordingly or to clarify why patients with a known immunodeficiency are still allowed in this study.

Coordinator Comment:
Primary immune deficiency represents only a minority of all people suffering from defects in normal immune reactivity : Yes, but the problem here is that this will be given to cancer patients who are mostly immunodeficient, even more so for metastatic patients. It is important to remember that these patients need to be careful when at the hospital for treatment or follow up visits to STAY AWAY from other patients who are vulnerable.
If you exclude on the basis of immunodeficiency then you may lose many of the cancer patients. I recognize that you have been discussing primary immunodeficiency (easy to exclude from the trial as it is highly unlikely) but you cannot treat cancer patients and then exclude them if they are immunodeficient due to prior treatments or their disease state.

Document B_BE_21_BVW7_Part 1A_VSV-GP-CAF P30 point 2: Reversion of VSV-GP to wild type VSV is certainly rare, but not impossible.

SBB Comment:

Indeed, reversion of VSV-GP back to a wild type VSV cannot be rule out but it would be almost impossible since the whole VSV-G sequence of the wt VSV has been removed in the current BI 1831169 genome and a co-infection of permissive cells in humans for VSV is highly unlikely as Europe is not an endemic area for VSV.

Document B_BE_21_BVW7_Part 1A_VSV-GP-CAF P30 "Based on the above, the consequence for integration into the host genome and horizontal transmission to other humans is considered negligible." The main risk in terms of transmission to other humans rests on the fact that the virus is replication competent.

SBB Comment:

According to the VSV Pathogen Safety Data Sheet of Public Health Agency of Canada (http://www.phac-aspc.gc.ca/lab-bio/res/psds-ftss/stomatit-eng.php), there is no documented evidence of human-to-human transmission for wt VSV.

Coordinator Comment:

There is also no documented case against it.

Document B_BE_21_BVW7_Part 1A_VSV-GP-CAF P31 "the overall likelihood of clinical vector transmission to healthcare professional considering risk management strategies (Section 3.6) remains very low to negligible". It is certainly very low, but the main risk might involve close contacts such as family members.

SBB Comment:

See SBB comment above under section 3.7, comment 1 of this document.

Document B_BE_21_BVW7_Part 1A_VSV-GP-CAF P36

"Innate immune response is sufficient to prevent and contain viral infection". This statement is at least at variance with the statement that "Thomsen et al. show that adaptive immune responses, especially CD4+ T cells play a role in the protection against encephalitis". Probably as well innate as adaptive immune responses can contribute to contain viral infection

SBB Comment:

The potential of immune response, is considered to be a patient safety related concern, which is addressed within the clinical assessment of the proposed trial and goes beyond the scope of the environmental risk assessment or the biosafety assessment of the proposed trial.

Coordinator Comment:

The statement "Innate immune response is sufficient to prevent and contain viral infection" is False – this is not true as a blanket statement. It is also a stupid comment if it is in the CAF and should be removed.

Comment 2

In the B_BE_21_BVW7_Part 1A_VSV-GP-CAF document concerning « COMMON APPLICATION FORM FOR VIRAL VECTORS CONTAINED IN INVESTIGATIONAL MEDICINAL PRODUCTS FOR HUMAN USE »

p36. A.3 Overall risk evaluation and conclusions :

Environmental safety data (shedding and biodistribution) performed in healthy and tumour-bearing mice, in dogs and in rabbits show that the risk of viral shedding and transmission is considered minimal, and that BI 1831169does not represent a risk even in livestock as revealed by pathogenicity studies in pigs (see Section 2.18).

Comment : In the case of direct inoculation of BI 1831169 to pigs experiments, the absence of observable symptoms of infection and no detectable shedding were reported. But, that doesn't mean that there are no other adverse effects for the health of the treated pigs.
Considering these pathogenicity studies in pigs, especially in regards to the few number of pigs used in n00282980 study (5 + 5 males), please consider the data coming from these studies as an experimental limited scale approach leading to extrapolated conclusions about the absence of adverse effects of the treatment, but without absolute certitude.
Therefore, in current stage of knowledge, the « absolute Zero risk » cannot be claimed; please correct the sentence and change it to a negligible or a very low risk…

SBB Comment:
If also deemed relevant by the coordinator, the expert's comment above could be rephrased towards the notifier as follows:
The notifier claims in section A.3 of the CAF that "BI 1831169 does not represent a risk even in livestock as revealed by pathogenicity studies in pigs". Although intradermal inoculation of VSV or VSV-GP in the apex of the snout of pigs was apathogenic and no shedding was detected, this does not mean that there are no other adverse effects on the health of the treated pigs. Furthermore, since VSV infection occurs primarily in domesticated livestock and only a small number of healthy pigs were used in the study (10), extrapolated conclusions about the absence of adverse effects of the treatment should be removed. Therefore, the notifier could be asked to clarify the risk as negligible or very low.

Coordinator Comment:
Coordinator agrees with all points mentioned in the comment of the expert

Comment 3
Has evaluated this item and has no questions/comments.

Comment 4
The consequences of horizontal transfer of the IMP to immuno-compromised people, pregnant women and children has not be evaluated.
VSV is a vector-borne virus, the likelihood that an insect may transmit the viral vector to another individual or animal upon a blood meal from an immunised person should be assessed.
The risk of accidental self-injection of the IMP by medical staff should be assessed.

SBB Comment:
See SBB comments above under section A2, comment 1; section 3.6, comment 4; section 3.7, comment 1 of this document respectively.

6. OTHER INFORMATION

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

Comment 1

General Remark. This release of an investigational medicinal product in a phase first in human context is extremely interesting and might lead to a form of therapy that could contribute significantly to the therapy of cancer. One has however to be aware of the apprentice sorcerer aspect of the approach. Indeed, the integration of the LCMV WE-HPI glycoprotein binding to ubiquitously expressed cell-surface receptors allows VSV-GP to infect many cell types not only in humans but also in other species. It is hoped that the interferon mediated reactions protect non-cancer cells, but that a deficiency in the interferon response makes cancer cells more vulnerable to the VSV-GP virus. This deficiency in the interference response of cancer cells occurs certainly not in all types and cases of cancer and rests on certain changes in signal transduction pathways such as an activation of the RAS/Raf1/MEK/ERK pathway (Noser et al., 2007) or a knock out of the Jak/Stat pathway (Le et al., 2020). However, it is certainly possible that in some tissues or organs, also in subgroups of "healthy" persons that do not suffer from (clinical detectable) cancer, similar activations or deactivations of signal transducing pathways occur or operate. This might render these persons vulnerable to the VSV-GP virus in case this virus succeeds in escaping from the phase1 trial and could result in serious health problems for these persons. These persons might also spread the virus to other humans. This means that the proposed phase1 first in humans release of the VSV-GP virus caries a risk that is orders of magnitude higher than the risk associated with releases of other genetically modified organisms that are not replication competent or do not carry the pathogenic cytotoxic potency (on which the anti-cancer effect rests) associated with the VSV-GP virus. This does not mean that the phase1 trial with VSV-GP virus should be forbidden, but it indicates that extremely efficient safety measures should be taken to prevent the spread of VSV-GP before more knowledge on the effect of the release of the virus is available. In particular the participating patients should be fully informed of these risks and in the selection of these patients their capacity to deal with this knowledge and problem should be taken into account.

SBB Comment:

The potential of interfering with the interferon signalling pathway is considered to be a patient safety related concern, which is addressed within the clinical assessment of the proposed trial and which goes beyond the scope of the environmental risk assessment or the biosafety assessment of the proposed trial. Human-to-human transmission has not been documented yet for wt VSV. Exposure of non-target individuals (e.g. by accidental exposure of heath care professionals at clinical trial site; by exposure of close contacts because of shedding) cannot be excluded. However, these non-target individuals will be exposed to much lower amounts of the drug product compared to the clinical dose. One should be cautious with the risk qualification. If risks are deemed significant or considerable, it would mean that an actual risk has been identified. In an environmental risk assessment context, the term 'risk' refers to a threat to the environment or human health. A 'possibility' or 'likelihood of occurrence', or 'unidentified uncertainty' is only one element leading to the determination of the risk. According to the EMA guideline on environmental risk assessment for medicinal products consisting of, or containing, genetically modified organisms (EMEA/CHMP/BWP/473191/2006 – Corr), the risk associated to the use of an investigational medicinal product is determined by the combination (or product) of the magnitude of the adverse effect and the likelihood of occurrence of such an adverse effect.

Inherent to the proposed FIH study, it is agreed that a level of uncertainty remains on the safety and possibility of replication and shedding upon IM administration of VSV-GP in human beings. In this regard, the proposed study allows for collecting data on all of this three aspects. These data will inform whether the shedding profile of VSV-GP, as demonstrated through the non-clinical studies conducted in mice, rabbits, dogs and pigs will be confirmed. Patients will be instructed to follow precautionary measures so as to limit exposure of non-treated individuals and the environment.

Coordinator Comment:
Coordinator agrees with the fact that the participating patients should be fully informed of these risks and thinks it needs to be emphasized. These patients will likely pass other cancer patients when they go to the hospital…

Information for the public NL p3 en p5"maar is tegelijkertijd in staat om aanhoudende antitumorale immuun responsen te induceren," "kan adaptieve immuunresponsen stimuleren die tegen de tumor gericht zijn" Do we have solid data concerning this induced immune response, and do we understand how it comes about, the mechanisms?

SBB Comment:
The recombinant VSV-GP virus is carrying the LCMV glycoprotein instead of the native VSV glycoprotein. The oncolytic virus VSV-GP is designed to be replication competent, and its intent is to infect, replicate in and kill interferon deficient cancer cells (section B, 10/39 in CAF_VSV-GP).
Since the wt VSV is sensitive to type I IFN responses, it preferentially replicates in cancer cells.
The chimeric VSV-GP virus has been engineered so that it lacks its natural neurotoxicity while retaining potent oncolytic activity (Muik et al, Cancer, Res, 2014).

Information for the public NL p4 "Hierna kunnen ze het ziekenhuis verlaten en worden ze geadviseerd om voorzorgsmaatregelen voor de bioveiligheid te nemen, sommige gedurende 10 dagen na de behandeling, en andere gedurende de hele behandelingsduur." How comes this difference and how this approach is justified?

SBB Comment:
According to section 3.6.g of the CAF, some recommendations given to clinical trial subjects to prevent dissemination such as washing hands, covering the injection site, wearing gloves when changing dressing(s), collecting of potentially soiled waste will have to be followed from C1D1 until the end of end of treatment visit (for Part 1 patients) or until C5D1 (for Part 2 patients). Whereas, other recommendations, such as avoiding close contact with young children, pregnant women, immunocompromised people and livestock will have to be followed for 10 days after each administration of BI 1821169. The notifier is requested to clarify why not all instructions are to be followed until the end of end of treatment visit or until C5D1 and how they justify these differences.

Comment 2
None

Comment 3
None

Comment 4
None

Typos and other errors/omissions

CAF, p19/40: administration of 1.4x108 TCID50 or 1.4x107 TCID50 […] administration of a single i.t. of 1.4x108 TCID50 : For clarity, the notifier could be requested to correct 108 and 107 into 10e8 and 10e7.

CAF, p19/40: section “Biodistribution and shedding in rabbits” : a single i.v. dose of 5.1x109 TCID50 : For clarity, the notifier could be requested to correct 109 into 10e9

CAF, p19/40: section “Shedding in dogs” : combination of 5x109 TCID50 s.c. and 1.5x1010 TCID50 i.v. in healthy beagles : For clarity, the notifier could be requested to correct 109 and 1010 into 10e9 and 10e10

CAF, p20/40: section “Pathogenicity and shedding in livestock” : with 1x107 TCID50 VSV or VSV-GP : For clarity, the notifier could be requested to correct 107 into 10e7

CAF, p21/40: Address : 12000 WSL should be corrected into 1200.

References

E Chare et al., Phylogenetic analysis reveals a low rate of homologous recombination in negative-sense RNA viruses, Journal of General Virology (2003), 84, 2691–2703

A Muik et al., Re-engineering vesicular stomatitis virus to abrogate neurotoxicity, circumvent humoral immunity, and enhance oncolytic potency, Cancer Res. 2014 Jul 1;74(13):3567-78

G Wollmann et al., Lassa-Vesicular Stomatitis Chimeric Virus Safely Destroys Brain Tumors, Journal of Virology, 2015, 89:13, 6711-6724

A R Thomsen et al., Cooperation of B cells and t cells is required for survival of mice infected with vesicular stomatitis virus, International Immunology. 1997, 9:11: 1757-1766

Compilation of the expert's evaluations of the answers of SCS Boehringer Ingelheim on the list of questions for dossier B/BE/21/BVW7

02 May 2022
Ref. SC/1510/BAC/2022_0516

Coordinator: Karen Willard Gallo (Institute Jules Bordet)
Experts: Anton Roebroek (KULeuven), Willy Zorzi (ULiège), Nicolas Van Larebeke (UGent), Aline Baldo (SBB)
SBB: Sheela Onnockx

INTRODUCTION

Dossier **B/BE/21/BVW7** concerns a notification from SCS Boehringer Ingelheim for a clinical trial entitled "Phase I open-label, dose escalation trial of BI 1831169 monotherapy and in combination with ezabenlimab in patients with advanced or metastatic solid tumors".

On 07 February 2022, based on a list of questions prepared by the BAC (SC/1510/BAC/2022_0160), the Competent Authority requested the notifier to provide additional information about the notification. The answers from the notifier to these questions were received by the Competent Authority on 11 April 2022. This complementary information was reviewed by the coordinator and the experts in charge of the evaluation of this notification.

Evaluation Expert 1

I understand that in most cases the innate immunity is sufficient and that the selectivity for cancer cells rests on this phenomenon. However, this does not imply that the adaptive immunity does not contribute to the protection against the virus.

SBB's and coordinator's Comment:
The innate immunity response alone is not sufficient to prevent and contain viral infection. Both innate and adaptive immune responses are required. Since the sentence "Innate immune response is sufficient to prevent and contain viral infection" is still present on page 37/41 in the CAF, the notifier could be requested to adapt this sentence by clearly indicating that both innate and adaptive immune responses are required to prevent and contain viral infection.

As to shedding I think that a rigorous assessment should be made to exclude any shedding after the treatment cycle

SBB's Comment:

The dissemination in any form into the environment via excreta (urine, feces, sweat, saliva, nasopharyngeal fluids), skin, blood and semen from the treated patient cannot be totally excluded. Therefore, the assessment of data on shedding will greatly contribute to the environmental risk assessment because it characterizes one of the first steps of the chain of events leading to potential transmission to people other than the patient or animals. A proper assessment of the likelihood of transmission necessitates an assessment of the likelihood of shedding of functional viral vector particles, the capacity for functional viral vector particles to retain their infectivity in the environment, the route of transmission to other people or animals, the capacity of the viral vector to infect cells of other persons or animals and the potentially adverse effects for other people exposed to a (limited) amount of viral vectors as compared to the therapeutic dose administered to patients by direct injection. It is remarked that not all of these steps contributing to a possible event of transmission can be documented by experimental data associated with a specific investigational medicinal product prior the start of a clinical trial. This is why the assessment of shedding also relies on a weight-of evidence approach whereby literature data on similar virus vector are taken into account as appropriate.

"We agree that based on the study design and the number of animals we can consider the risk for livestock to be negligible. The section A.3 of the CAF has been updated accordingly".
It should be "very low" instead of "negligible"

SBB's Comment:
An estimate of risk is obtained from a consequence and a likelihood that a hazard will be realized. Different component may be differently weighted. In its answer the notifier points to the fact that the pig has been used as a model previously used in environmental risk assessment, to the absence of clinical signs during the complete duration of the pig study, and to the lower potential of herd spread. While the potential of spreading could be considered very low, it may be considered that the overall risk to livestock is negligible as no clinical signs were observed during the study.

Question 24 The procedure proposed by BAC should be included in full text

SBB's Comment:
Although the entire procedure has not been described in the CAF document, it has been done in the HCP Guide for the medical personnel.

Evaluation Expert 2

In the « 2020-003902-30_VSV-GP-CAF-TC » document of this dossier » :
Page 23 of 41 :
It is written that : « Physical inactivation: BI 1831169 is inactivated by heating (60°C, 30min). »
Please precise the conditions of heating : 60°C heating in humidified or dried air conditions ? » or incubating into a water bath?

Evaluation Expert 3

In my opinion the notifier addressed correctly and satisfactorily the comments/questions that we have raised in January 2022

Evaluation Expert 4

J'ai lu les réponses du notifiant et je n'ai pas de remarques.