Adviesraad voor Bioveiligheid
Conseil consultatif de Biosécurité

Advice of the Belgian Biosafety Advisory Council on the notification B/BE/21/BVW6 of the company GlaxoSmithKline Biologicals SA for deliberate release in the environment of genetically modified organisms other than higher plants for research and development

Final version – 23/02/2022
Ref. SC/1510/BAC/2022_0243

Context

The notification B/BE/21/BVW6 has been submitted by GlaxoSmithKline Biologicals SA to the Belgian Competent Authority in November 2021 for a request of deliberate release in the environment of genetically modified organisms other than higher plants for research and development according to Chapter II of the Royal Decree of 21 February 2005.

The planned activity concerns a clinical trial and the title of the notification is: ***"A phase 2, single-blinded, randomized, controlled multi-country study to evaluate the safety, reactogenicity, efficacy and immune response following sequential treatment with an antisense oligonucleotide (ASO) against chronic Hepatitis B (CHB) followed by chronic Hepatitis B targeted immunotherapy (CHB-TI) in CHB patients receiving nucleos(t)ide analogue (NA) therapy".***
The proposed vaccination regimen comprises the use of two viral vaccines with hepatitis B surface antigens developed as a novel therapeutic Hepatitis B Virus (HBV) vaccination strategy to induce robust T-cell response and/or antibody response against various HBV antigens (HBsAg). The aim is to restore the patients' immune control of HBV infection and to achieve functional cure, defined by loss and ultimate clearance of HBsAg, in order to allow patients to safely discontinue NA therapy. The investigational therapeutic HBV vaccines consist of a recombinant replication-defective Chimpanzee Adenovirus vector (ChAd155) encoding a fusion of sequences derived from two HBV proteins (ChAd155-hIi-HBV) and a highly attenuated orthopoxvirus Modified Vaccinia Virus Ankara (MVA), replication-deficient in humans and other mammals, with the same antigens-encoding transgene resulting in the viral vaccine MVA-HBV. The antigens-encoding transgene is a fusion of sequences encoding hepatitis B proteins HBc (core nucleocapsid protein) and HBs (small surface antigen), which are separated by a 2A self-cleaving region of the foot and mouth disease virus for processing of the HBc and HBs into separate proteins. In the ChAd155, the N-terminal part of the gene encoding the HBc protein in the transgene has been fused to the gene encoding the human Major Histocompatibility Complex (MHC) class II-associated invariant chain p35 isoform (hIi) that is acting as a genetic adjuvant to the associated antigen and will help inducing a more robust HB antigen-specific immune response in the host.
In this Phase 2 study, the heterologous prime-boost regimen consist in the intramuscular administration of $5x10^{10}$ viral particles of ChAd155-hIi-HBV (prime) and 2×10^{8} plaque forming unit of MVA-HBV

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(boost) in a sequential manner, with subsequent administration of two doses of antisense oligonucleotide (ASO).

It is planned to conduct this study at two clinical sites located in the Flemish Region. A total of 184 patients will be enrolled in the study, with up to 7 patients in Belgium.

The use of the GMOs in a clinical trial has already been assessed by the BAC in the framework of notifications B/BE/18/BVW4[1], also submitted by GlaxoSmithKline Biologicals SA.

The dossier has been officially acknowledged by the Competent Authority on 22 November 2021 and forwarded to the Biosafety Advisory Council (BAC) for advice.
Within the framework of the evaluation procedure, the BAC, under the supervision of a coordinator and with the assistance of its Secretariat, contacted experts to evaluate the dossier. Two experts from the common list of experts drawn up by the BAC and the Service Biosafety and Biotechnology (SBB) of Sciensano answered positively to this request. The SBB also took part in the evaluation of the dossier. The experts and the SBB assessed whether the information provided in the notification was sufficient and accurate in order to state that the deliberate release of the genetically modified organism 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 experts.

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

On 21 December 2021, 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 07 February 2022 and transmitted to the secretariat of the BAC the next day. This complementary information was reviewed by the coordinator and the experts.

In parallel to the scientific evaluation of the notification, the Competent Authority also made the dossier available on its website for the one-month public consultation foreseen in the abovementioned Royal Decree. The Competent Authority received no reactions from the public.

Summary of the scientific evaluation

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

[1] Advice of the Belgian Biosafety Advisory Council on the notification B/BE/18/BVW4 - *Ref. SC/1510/BAC/2018_0767*

The donor, recipient and parental organisms were found to be adequately described in the dossier.

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

Upon a remark of the BAC, the notifier corrected the location of an element that was depicted erroneously in a schematic figure representing a plasmid carrying the genetically modified ChAd155 viral genome. Other molecular characteristics of ChAd155-hli-HBV and MVA-HVB including phenotypic and genetic stability of the transgenes were found to be adequately described in the dossier.

3. The conditions of the release

With respect to the measures to be taken by the personnel during manipulations of the GMOs, in particular with respect to manipulations likely to generate aerosols, the notifier was asked to improve the Biosafety instructions for site staff with additional biosafety instructions. The remarks of the BAC were adequately implemented in the updated document.

The other information provided on the conditions of release has been assessed previously and the BAC is of the opinion that there are no other concerns.

4. The risks for the environment or human health

The notifier states that shedding of ChAd155-hli-HBV into the environment will be limited given the experience build with intramuscular (IM) injection of other replication deficient adenoviral vectors and data obtained with IM injection of ChAd155-hli-HBV in Sprague-Dawley rats. Upon a question of the BAC to give an update on the shedding data that are being collected for ChAd155-hli-HBV in the context of TH HBV VV-031 HBS:001 (an ancillary study of the main study TH HBV VV-001) (clinical trial 2017-001452-55 (Biosafety dossier B/BE/18/BVW4), the notifier referred to the protocol for detailed information on the nature of the samples taken, the timepoints, the limit of detection and lower limit of quantification. The notifier informed that study results will be made available by mid year 2022. Meanwhile, in its dossier, the notifier also refers to the shedding data obtained with another E1/E4-deleted replication-defective chimpanzee-derived adenoviral vector (ChAd3) carrying a transgene encoding a hepatitis C virus protein (NSmut) given the homology between the ChAd3-NSmut and ChAd155. In this respect, the BAC holds his position on the limited relevance of shedding data obtained with ChAd3 to conclude on the shedding properties of ChAd155-hli-HBV [2]. On the other hand the BAC acknowledges that on the basis of a review of biodistribution studies of several adenoviral vector backbones administered via the intramuscular route, it can be anticipated the vector may have a similar shedding profile.
The probability of shedding of ChAd155-hli-HBV vaccine cannot be excluded and adenoviruses are relatively persistent and may survive outside of the body for prolonged time. At the other hand, adenoviruses are susceptible to common desinfectants.
Furthermore, the BAC made a few remarks on the notifier's assessment of ChAd155-hli-HBV, which the notifier instructions adequately implemented in the updated documents making part of the dossier.

[2] Advice of the Belgian Biosafety Advisory Council on the notification B/BE/18/BVW4 - *Ref. SC/1510/BAC/2018_0767*

The probability of recombination, for example upon administration of ChAd155 to a trial participant, is judged to be very low by the notifier due to the lack of sequence homology between the human E1 flanking regions of human Ad5 and chimpanzee adenovirus E. Building on the experience of the BAC with the evaluation of the potential and the outcome of recombination of another simian adenovirus belonging to serotype E that are deleted for E1 and E3 and that harbors the E4 region of hAd5, it was concluded by the BAC that recombination events with this recombinant simian adenovirus, if it occurs, would likely not lead to any additional environmental risk as compared to circulating wild-type hAd5 adenoviruses. Furthermore, with respect to the probability for recombination with wild-type adenovirus, the BAC acknowledges Wold and Toth, 2013[3] concluding that recombination events between replication-deficient adenoviral vectors have not been reported and if these were to occur, these would not lead to replication-competent viruses expressing the transgene.

Given the replication-defective properties of the vector, the low probability of shedding, and the fact that no recombination events have been reported so far with E1/E4-deleted replication-defective vector, the BAC concludes that the risk for the environment and human health associated to possible shedding of the vector, if it were to occur, is low.

After having received the updated 'Biosafety instructions for site staff' the BAC further remarked that the description of the procedures for the management of accidental spills in the still leaves room for improvement and recommend to add the following procedure:
In case of accidental spills or breakage of a vial containing the GMO, people in the area of the spill should be alerted and asked to leave the area. All personnel involved with the spill should remove contaminated clothes before leaving the area. The area should be closed and a message "DO NOT ENTER" should be posted. After 30 min, the area can be entered again by wearing a clean lab coat, disposable gloves, glasses, disposable shoe covers and a mask. The spill should be covered with towels or other absorbent material starting from the edge toward the centre. Appropriate disinfectant should be poured over the absorbent material starting from the edge to the centre. Sufficient contact time should be allowed so as to ensure inactivation of the GMO by the disinfectant. After that, the paper towels and broken vials should be removed with tongs or forceps and discarded in a biohazard waste bag. The PPE should be discarded in the biohazard bag. The lab coat should be decontaminated before disposal. The medical staff should report the incident to the responsible of the site.
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, shoe covers, mask), tongs or forceps in order to take broken vials, absorbent paper towels, biohazard waste bags.

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

To meet the concern of the Biosafety Advisory Council on the appropriateness of using 70% ethanol in case of spilling of ChAd155-hli-HBV, which is a non enveloped adenoviral vector, the notifiers amended the "Biosafety instructions for site staff' so as to specify the use of a solution of 1% sodium hypochlorite, 2% glutaraldehyde or 5% phenol with a minimal contact time of 20 minutes. The BAC further recommends to indicate the use of phenol derivatives or phenolic compounds instead of 5% phenol because of the corrosive properties and potential systemic toxicity of phenol.

[3] Wold, W& Toth, K. Adenovirus vectors for gene therapy, vaccination and cancer therapy. *Curr. Gene Ther.* 2013, *13*, 421-433

Conclusion

Based on the scientific assessment of the notification made by the Belgian experts, the Biosafety Advisory Council concludes that it is unlikely that the investigational therapeutic HBV vaccines ChAd155-hli-HBV and MVA-HBV will have any 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 dossier submitted in November 2021 and in the following new or updated documents provided on 07 February:

- 2021-003567-10-Biosafety instructions for site staff (27 Jan 2022)
- 2021-003567-10_Annex II ChAd155-hli-HBV (January 2021), and 2021-003567-10_Annex II ChAd155-hli-HBV_without confidential information (January 2022).
- 2021-003567-10_Annex IIIA_ChAd155-hli-HBV (January2022) (and in the nonconfidential part)

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

- The notifier and the investigators must strictly apply the clinical trial protocol, and all the safety instructions as described in the dossier and the new or updated documents. Furthermore, the notifier is recommended to improve, in the document 'Biosafety instructions for site staff", the description of procedures for study staff regarding the management of accidental spills or breakage of a vial containing the GMO (see text proposal in section 4 of this advice). Furthermore, the indication of 5% phenol as desinfectans should be avoided (see section 5 of this advice).

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

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

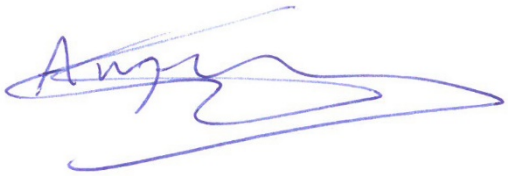
- At the latest 15 days after the start of the trial, the notifier should provide, along with the delivery of the control sample, a detailed protocol for the method of conservation and analysis of the control sample.

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

- At the latest six months after the last visit of the last patient included in the trial, the notifier must send to the competent authority at the attention of the Biosafety Council a report with details concerning the biosafety aspects of the project. This report will at least contain:
    - The total number of patients included in the trial and the number of patients included in Belgium;

- A summary of all adverse events marked by the investigators as probably or definitely related to the study medication;
- A report on the accidental releases, if any, ChAd155-hli-HBV and MVA-HBV.

- The notifier must provide a report of the shedding data obtained from TH HBV VV-031 HBS:001 (an ancillary study of the main study TH HBV VV-001) (clinical trial 2017-001452-55 - Biosafety dossier B/BE/18/BVW4), which was announced to be made available by mid year 2022.



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/BVW6 (ref. SC/1510/BAC/21_1270)

Adviesraad voor Bioveiligheid
Conseil consultatif de Biosécurité

Compilation of comments of experts in charge of evaluating the dossier B/BE/21/BVW6 And comments submitted to the notifier

21 December 2021
Ref. SC/1510/BAC/2021_1270

Mandate for the Group of Experts: Mandate of the Biosafety Advisory Council (BAC) of 16 November 2021.
Coordinator: Jozef Anné (KUL)
Experts: Anton Roebroek (KULeuven), Nicolas van Larebeke-Arschodt (UGent, VUB), Amaya Leunda (SBB)
SBB: Katia Pauwels

INTRODUCTION

Dossier **B/BE/21/BVW6** concerns a notification of the company GSK Biologicals SA for deliberate release in the environment of genetically modified organisms other than higher plants according to Chapter II of the Royal Decree of 21 February 2005.
The notification has been officially acknowledged on 22/11/2021 and concerns a phase II clinical trial involving the administration of Hepatitis B virus (HBV) viral vectored vaccines (ChAd155-hIi-HBV and MVA-HBV) and adjuvanted proteins vaccine (HBc-HBs/AS01B-4), together denominated as GSK3528869A, to chronic Hepatitis B patients.
GSK3528869A was already notified by GSK Biologicals SA in July 2018 in dossier B/BE/18/BVW4 (see BAC advice of 01/10/2018, ref. SC/1510/BAC/2018_0767). The deliberate release of a GMO using the same ChAd155 viral vector backbone was also notified in dossier B/BE/18/BVW 9 (see BAC advice of 22/01/2019 ref. SC/1510/BAC/2019_0078).

♦ INSTRUCTIONS FOR EVALUATION

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

List of comments received from the experts

Remark: The comments below have served as basis for a list of questions that the Competent authority forwarded on 21-12-2021 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.

List of comments/questions received from the experts

1. INFORMATION RELATED TO THE CHARACTERISTICS OF THE DONOR, THE RECIPIENT OR PARENTAL ORGANISM
(e.g. possibility of natural transfer of genetic material to other organisms, pathological, ecological and physiological characteristics, indigenous vectors …)

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

On ChAd155-hli-HBV:

P16. Testing for replication competent adenoviruses should occur through a technique that allows the detection of rare species of the virus. I think to have understood that the detection of replication competent adenoviruses rests on the presence of virus-induced cytopathic effects after 28 days in culture. Does this test have a sufficient reliability, allowing to exclude that external factors could inhibit the establishment of a cytopathic effect ?

SBB comment

P 17 Annex IIIA_ChAd155-hli-HBV (August 2021) reports on the extended *in vitro* virus-induced cytopathic effect assay performed at different stages of the manufacturing process.
Detection of replication-competent viral vectors is generally performed by an infectivity assay on sensitive detector cell lines, which are not able to complement for the genes deleted from the vector. Other indicators of viral replication may be used as appropriate. When replication-competent viral vectors are not supposed to be present in the test sample, considering vector construction and cell lines used, at least 2, but preferably 3 or 4 successive passages are performed on the detector cell line, where applicable. Detection of a cytopathic effect at the end of the passages reveals the presence of replication-competent viral vectors in the preparation. Positive controls are included in each assay to monitor its sensitivity.
An assessment of these processes, and more particularly the assessment of the potential of formation of replication-competent adenoviruses (RCA) in the manufactured lots prior to administration to the patient, is part of the quality control assessment.
The requirements for RCA testing is likely to be determined by the European Pharmacopoeia and is within the remit of the quality control assessment of the clinical trial application.
(see https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-quality-non-clinical-clinical-aspects-live-recombinant-viral-vectored-vaccines_en.pdf)

An evaluation of the potential of *in vivo* formation of replication-competent adenoviruses and potential associated risk is covered in section III.1.c. and IV.1.c. of Annex IIA_ChAd155-hli-HBV (August 2021): *a remaining risk of RCA formation would be post-release in the event of recombination of the GMO with human adenovirus where the study subject receiving the vaccine is co-infected by human adenovirus. However, the probability of homologous recombination between the ChAd155 viral vector and the human Ad5 E1 region of the host cell is considered very low, due to the lack of sequence homology between the human E1 flanking regions of human Ad5 and chimpanzee adenovirus E1. The use of codon-optimized transgene sequence reduces further the probability of recombination with wild-type sequences. The risk of RCA is therefore considered low.*

Coordinator comment

A similar answer was given for ChAd155-RSV: Absence of replication competent adenovirus (RCA): The risk of occurrence of the formation of RCA from homologous recombination between the ChAd155 viral vector and the human Ad5 E1 region of the host cell is considered very low, due to the lack of sequence homology between the human E1 flanking regions of human Ad5 and chimpanzee adenovirus E1. It has been shown that recombination and production of RCA does not occur when they are propagated in HEK-293 cells (Colloca *et al*. 2012), thus eliminating the problem of RCA generation during the adenovector manufacture.

With respect to the probability for recombination with wild-type adenovirus, the BAC acknowledges Wold and Toth, 2013 concluding that recombination events between replication-deficient adenoviral vectors have not been reported and if these were to occur, these would not lead to replication-competent viruses expressing the transgene (cfr Advice of the BAC on the notification B/BE/18/BVW4 of the company GlaxoSmithKline Biologicals SA, *Ref. SC/1510/BAC/2018_0767)*

Part MVA-HBV:

P12 “Following infection by MVA, non-infectious immature virions and abnormal particles are produced but no infectious particles.”
How good is the evidence for this as MVA has not lost all of the capacity to replicate?

SBB comment

The expert’s comment relates to p12 of 2021-003567-10 Annex IIIA_MVA-HBV (August 2021).
For many aspects associated to the environmental risk assessment of MVA-HBV (see 2021-003567-10 Annex IIA_MVA-HBV (August 2021), the notifier is referring to two (SBB) publications Verheust *et al*., 2012 and Goossens *et al*., 2013, which review biosafety aspects of MVA-viral vectors used for gene therapy and vaccination. MVA viral vectors are highly attenuated vectors that are not able to replicate in most mammalian cells. Table 2 in Verheust *et al*., comprises a list of permissive, semi-permissive and non-permissive cells or cell lines (including cells or cell lines of human origin).

P14 “There is no transfer of genetic material from the donors to their natural hosts”. I am not certain that this never occurs.

SBB comment

For clarification : the expert s' comment relates to p14 of 2021-003567-10 Annex IIIA_MVA-HBV (August 2021), in which the notifier used the following nomenclature
- The donor organism: the organism(s) from which the sequences encoded by the GMO are derived
- The recipient organism: the engineered vector with an "empty" cassette (i.e. without the transgene)
- The parental organism: the organism from which the engineered vector is derived

Comment 3

Has evaluated this item and has no questions/comments.

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

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Part ChAd155-hli-HBV:

Has evaluated this item and has no questions/comments.

Part MVA-HBV:

P20 "*MVA is highly attenuated, replication deficient and has negligible likelihood of mobilization. Its release is restricted to the delivery via the intramuscular route of administration to human study subjects in a highly controlled clinical trial setting*".
In fact the vaccinated people will mix with the general population. But the risk of recombination seems indeed very low.

Comment 3

Has evaluated this item and has no questions/comments.

3. INFORMATION RELATED TO THE CHARACTERISTICS OF THE GMO

3.1. Information related to the genetic modification
(e.g. methods used for the modification, description of the insert/vector construction ...)

Comment 1

In document '2021-003567-10_Annex IIIA_ChAd155-hli-HBV (August 2021)' on the pages 23 and 24 of 59 in figure 3 and the table an element is mentioned/indicated. Can an explanation be given why this element is present in the GMO (downstream of the left LTR)?

Comment 2

Part ChAd155-hli-HBV and Part MVA-HBV:

Has evaluated this item and has no questions/comments.

Comment 3

In 2021-003567-10_AnnexII_ChAd155-hli-HBV (August 2021) p6 - 2. Characteristics of the GMO a. description of the GMO and doses;
In 2021-003567-10_Annex IIIA_ChAd155-hli-HBV (August 2021) p11 - 1. Scientific name (a) Donor Part of the insert consists of a sequence encoding a truncated core protein (HBc): it is not clear what does "truncated" stand for ?

SBB comment

Section 2.4.1.2.3 in the 2021-003567-10_Investigator Brochure_edition5_TH_HBV (12 AYG 2021), p30/135 provides more information on the C-terminally truncated hepatitis B core protein :

Coordinator comment

The information is also illustrated in 2021-003567-10_Annex IIIA_ChAd155-hli-HBV (August 2021)' , Fig. 5 & 6 (p28)

3.2. Information on the molecular characteristics of the final GMO
(e.g. number of copies of the transgenes, phenotypic and genetic stability of the transgenes, expression of the new genetic material, re-arrangements in the genome, inclusion or suppression of genetic material ...)

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Part ChAd155-hli-HBV:

How specific is the transfection of the "targeted cells" ? To what extent can cells that should not be "targeted" still be transfected? The expert wonders whether the vaccine might affect cells that are not a target of Hepatitis B virus. This could possibly contribute to the risk of an immunologic reaction against such cells, leading to an autoimmune disease.

Coordinator comment

Not an biosafety issue

Can the additional atypical bands observed in Western blots have toxic or unwanted immunological effects?

Coordinator comment

The appearance of the additional bands are mentioned on p32 as "Several bands that appear at higher and lower molecular weights can be observed on both the HBc and the HBs blots; the HBs blot presents the most complex pattern. The identity of these bands is currently unknown"

Can variations in the post-translational processing of the transgene lead to unpredictable changes in the activity of the vaccine?

Coordinator comment

Not an biosafety issue

How certain is the absence of replication competent virus in the long run in the manufacturing lots?

Coordinator comment

See coordinator comments above under section 1. Comment 2 See comments above: The risk of RCA is considered low

On what rests the immune tolerance to the mli sequence? The expert supposes this tolerance is innate?

Coordinator comment

As concluded from animal experiments, no anti-mli antibodies and no mli-specific T-cells were detected in any animals at 2 weeks post-first or second immunization, suggesting that the immune tolerance to the mli sequence was preserved in mice receiving repeated vaccination with high dosage of the ChAd155-mli-HBV. (p35/59).

What is the exact reason to administer adjuvanted lyophilized HBc-HBs proteins? The expert wonders whether adjuvant activity, which includes the upregulation of certain proinflammatory cytokines and costimulatory molecules might contribute to the risk of autoimmune disease.

SBB comment

The proposed candidate chronic hepatitis B targeted immunotherapy (CHB-TI) including two viral vector vaccines coding for the HBc and the HBs antigens are aimed to induce a strong CD8+ T-cell response, and together with sequential or co-administration of AS01B-4-adjuvanted HBc-HBs protein vaccine to induce strong antigen-specific CD4+ T-cell and antibody responses (see for example p25 of the Investigator's brochure).
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. Given the replication –deficient properties of ChAd155-hli-HBV and the low potential of shedding after

IM administration, the potential of generating autoimmune disease or unwanted immunologic effects, 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

Agrees with SBB comment, this goes beyond the scope of the environmental risk assessment or the biosafety assessment of the proposed trial.

With respect to the comment on absence of RCA , see *SBB and coordinator comment* above under section 1, comment 2 of this document.

Part MVA-HBV:
How can we be certain that, during the mass production process, no unwanted sequences possibly giving rise to unwanted proteins are picked up and present in a fraction of the vaccine in some lots?

Coordinator comment

Quality control will be carried out as explained in the dossier (see p29 *(d) purity of the insert from any unknown sequence and information on the degree to which the inserted sequence is limited to the DNA required to perform the intended function.*

Can the additional atypical bands observed in Western blots have toxic or unwanted immunological effects?

Coordinator comment

Not an issue as regards the molecular characteristics and potential impact on human health and the environment.

P29. "*Administration of GSK3228836 with sequential or co-administration of Th HBV vaccine regimens did not further overcome the immune tolerance to HBs antigen in our HBV chronic infection mouse model(AAV2/8-HBV transduced HLA.A2/DR1 mice). No further increase in HBs antibody or T-cell response was observed and there was no significant reduction of circulating HBs antigen levels in comparison to mice only immunized with the vaccine regimens or treated with GSK3228836 alone. Hepatic changes (typically seen with ASO treatments) were only observed when GSK3228836 and TH HBV vaccine regimens were combined, or in groups treated with GSK3228836 alone.*"

In view of this statement I do not see clearly the rationale for the proposed Phase 2 clinical trial (at least as based on the experimental results in animals).

SBB comment

In the protocol, section Study Rationale, p50 and p53, it is clarified that treatment with GSK3528869A aims to inhibit the synthesis of HBsAg to allow patients to safely discontinue NA therapy without virological or clinical relapse.
Of note, the assessment of the rationale for the proposed Phase 2 study from the perspective of the patient safety goes beyond the scope of the environmental risk assessment per se.

Coordinator comment

Agrees with SBB comment, the rationale for the proposed Phase 2 study from the perspective of the patient safety goes beyond the scope of the environmental risk assessment per se .

P31-32 Potential allergenic effects and Potential toxic effects were assessed, but no attention is paid to auto-immune reactions, which might be the most important severe health effects of any vaccination.) (e.g. KLok et al.,2021, Lancet haematology Nov 11 ; Zhou et al.,(2021) Front Immunol 121, 733418). Although a meta-analysis (Petras et al., 2021, Vaccines 9, issue 8) did not find an overall increase of the incidence of autoimmune diseases in association with vaccination it seems likely that vaccination can contribute to the emergence of an autoimmune disease. In mechanistic -terms such an association is possible involving a process called epitope or determinant spreading (Lehmann *et al.*, 1993; 1998; Pieters, 2003). Also the expert wonders whether adjuvant activity, which includes the upregulation of certain proinflammatory cytokines and costimulatory molecules might contribute to the risk of autoimmune disease.

SBB comment

The same SBB comment applies as above: Given the replication attenuated properties of MVA-HBV and the low potential of shedding after IM administration, the potential of generating autoimmune disease or unwanted immunologic effects (for example due to the potential presence of unwanted sequences or proteins), is considered to be both a quality aspect of the drug product and a patient safety related concern, both which are addressed within the quality and 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

Agrees with SBB comment. Interesting remark of the expert, but goes beyond the scope of the environmental risk assessment or the biosafety assessment of the proposed trial.

Comment 3

Has not evaluated this item

3.3. Considerations for human, animal or plant health
(e.g. invasiveness and virulence, toxic or allergenic effects, possibility of survival outside of receiving host, other product hazards ...)

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Part ChAd155-hli-HBV:

P38 "*Although the mechanism underlying these decreases currently remains unclear, it is well described in literature that, post intravenous administration, adenovirus activates platelets and induces platelet-leukocyte aggregate formation, causing an associated increase in platelet and leukocyte-derived micro-particles (Othman et al. 2007, Stone et al. 2007). "*
This is worrying. It makes you think of the thrombocytopenic thrombosis occurring after corona vaccination with an adenoviral vector-based vaccin.

The expert thinks that it might be advisable to test the presence of anti-CD74 antibodies in participants in tests with adenovirus vaccines, and to test parameters involved in blood clotting rather than only observing clinical effects.

SBB and 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. Given the replication –deficient properties of ChAd155-hli-HBV and the low potential of shedding after IM administration, the potential of activating platelets or platelet-leukocyte aggregate formation, 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

Agrees with SBB comment

The expert wonders whether we can be sure that no replication competent viruses arise after recombination with adenoviruses present in the subjects participating in a test protocol.

SBB and coordinator comment

See *SBB comment* above under section 1, comment 2 of this document.

Part MVA-HBV:
P38 That the GMO will be administered during a clinical study does not mean that the environment cannot be affected.

Coordinator comment

See p21. Also because of the severely restricted host range of MVA, its lack of virulence in animals, and its highly attenuated replication, we do not expect the vector to survive or spread in the environment.

Comment 3

In 2021-003567-10_Annex IIIA_ChAd155-hli-HBV (August 2021) (c) information on survival, including seasonability and the ability to form survival structures (c) Parental organism, p18

"Adenoviruses can survive for long periods on environmental surfaces, Annex II ChAd155-hli-HBV p17 : "There is also minimal risk of persistence or survivability of the GMO vector in the environment."

There are some discrepancies concerning capacity of survival and persistence into the environment of adenovirus (recipient and GMO). Sometimes, it is described as persistent and sometimes as unable to persist outside the host. For consistency along the documents, to check and correct where needed.

SBB comment

If also deemed relevant by the coordinator , the expert's comment above could be rephrased towards the notifier as follows:

There are some discrepancies concerning capacity of survival and persistence into the environment of adenoviruses (recipient and GMO). Sometimes, it is described as persistent and sometimes as unable to persist outside the host. For example, on p18 (section II.A.11.C: (c) information on survival, including seasonability and the ability to form survival structures) in 2021-003567-10_Annex IIIA_ChAd155-hli-HBV (August 2021) it is stated that "*Adenoviruses can survive for long periods on environmental* surfaces' whereas on p17 in 2021-003567-10_Annex II ChAd155-hli-HBV it is claimed that "*There is also minimal risk of persistence or survivability of the GMO vector in the environment."* For consistency reasons, the notifier is requested to correct/adapt the wording along the documents as appropriate.

Coordinator comment

I don't see (or overlooked) the problem
For the parental adenovirus strains, there are 2, (1) parental ChAd155 virus This parental organism, the ChAd155 from chimpanzees.and E4orf6 derived from human Ad5.
In the discussion of (2) the parental strains, in most cases for the adenoviruses the emphasis is on human adenoviruses., and not on ChAd155 virus. This could be made more explicit, but this is an editorial issue.

4. INFORMATION RELATING TO THE CONDITION OF RELEASE

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

Comment 1

The document '2021-003567-10_Biosafety instructions for site staff (17 SEPT 2021)' suggests that 70% ethyl alcohol can be used to inactivate the GMOs, e.g. upon spilling. For the enveloped MVA-based GMO this might be sufficient, but for the non-enveloped ChAd155-based GMO this is not. Like mentioned in BAC_2018_0767 dealing with a previously evaluated clinical trial using the same two GMOs, the 'Biosafety Instructions for site staff' should be updated with respect to the use of effective disinfectant (with particular attention for effective disinfectants for non-enveloped adenoviral vectors) and the use of personal protective equipment should be further specified. Also, the description of the procedures for the management of accidental spills still leaves room for improvement.

SBB comment

Like pointed out by the expert, the same question (including reference to scientific literature) was posed to the notifier by the BAC in the context of biosafety dossier B/BE/18/BVW4 involving the use of ChAd155-hIi-HBV and MVA-HBV. The question was as follows :
Of the two GMOs to be used as a vaccine, the recombinant vaccine vector Modified Vaccinia Ankara-HBV is an enveloped replication-defective virus, of which it indeed can be expected to be become efficiently inactivated by treatment with 70% ethanol in case of accidental spilling (Rabenau et al., 2010). For the recombinant vaccine vector ChAd155-hIi-HBV being a non-enveloped adenoviral vector this is questionable, although the document 'Biosafety instructions for site staff' suggests to use 70% ethanol in case of spilling ("In case of spilling of the vaccine/sample, the area should be decontaminated with 70% ethanol-soaked cloth with a minimal contact time of 1 min."). 70% ethanol has virucidal activity against adenoviruses, but is probably only efficient after prolonged exposure times (see e.g. https://digitalcommons.usu.edu/biology_posters/140/). Furthermore, there might be strain-related differences with respect to sensitivity (Iwasawa et al., 2012). Anyhow, laboratory protocols and biosafety guides for using adenoviral vectors state clearly that ethanol is not suitable to inactivate adenoviruses adequately (https://ehs.research.uiowa.edu/adenovirus-and-adenoviral-vectors, https://www.addgene.org/biosafety/). The document 'Biosafety instructions for site staff' should be updated and state clearly that in case of ChAd155-hIi-HBV suitable disinfectants like Virkon S, Umonium spray or a 1% solution of sodium hypochlorite should be used. Adenovirus is susceptible to: 0.5% Sodium hypochlorite, 2% Glutaraldehyde, 5% Phenol, or Autoclave for 30 minutes at 121°C under 15 lbs.

As a response to this comment for dossier B/BE/18/BVW4, the notifier amended the Biosafety instructions as suggested by the BAC (version 28 Aug 2018). Hence, along with the question/comment above, the notifier could be requested to adapt '2021-003567-10_Biosafety instructions for site staff (17 SEPT 2021)' like it was agreed upon for document ' 2017-001452-55 (BBE18BVW4)-10_Biosafety instructions for site staff (version 28 Aug2018)'.

Coordinator comment

Agreed

Comment 2

Part ChAd155-hIi-HBV and Part MVA-HBV

Has evaluated this item and has no questions/comments.

Comment 3

In document Biosafety instructions for site staff; Room set up / Waste management:
Applicant recommends the use of 70% ethanol for the decontamination of work benches and in case of accidental spills with the vaccine or patient samples.
In 2021-003567-10_Annex IIIA_ChAd155-hIi-HBV (August 2021) p18 : The applicant notes that ChAd155 viruses are susceptible to disinfectants active against enveloped viruses.

Adenovirus are not enveloped viruses and surfaces may not be decontaminated by disinfectants used against enveloped viruses.

Ethanol 70% is not suitable for inactivation of non-enveloped adenoviruses. Instead, it is recommended to use formaldehyde or chlorine based agents. For example, 1:5 dilution of bleach with 1 minute contact or 2 minutes contact with alcohol-based hand gels (Pathogen Safety Data Sheets, Health Canada)

In other parts of the annex, the information is correctly reported, for example in instructions on p47 "Adenoviruses are readily inactivated by a number of disinfectants active against non-enveloped viruses. They are however resistant to lipid disinfectants because they are non-enveloped."

For consistency, to check and correct where needed.

SBB comment

This comment is in line with comment 1 of section 4 here above. See also SBB comment in comment 1.
Like further pointed out by the expert, the notifier could be requested to correct 2021-003567-10_Annex IIIA_ChAd155-hli-HBV (August 2021) p18 so as to avoid any misunderstanding on the non-enveloped nature of adenoviruses.

Additional SBB comment

In the legend of Figure 9 (study design overview) in the document 2021-003567-10_Annex II ChAd155-hli-HBV (August 2021), it is stated that 'Dose regimen for GSK3228836 may be adjusted based on when data from study B-Clear (EudraCT number 2020-001083-29) are available '.
Could the notifier elaborate on the scope of study 2020-001083-29 ? Has this dossier been notified as a biosafety dossier? What is the dose regimen ?

Additional SBB comment

On p 15/27, 2021-003567-10_Annex II ChAd155-hli-HBV (August 2021), the notifier states that an ancillary shedding study (TH HBV VV-031 HBS:001) in a subset of subjects from the ongoing first trial in human clinical study (TH HBV VV-001) is being performed to evaluate viral shedding of the ChAd155-hli-HBV vaccine.
The notifier could be asked to detail the methodology that was used for conducting the shedding study by indicating the number of samples taken, the nature of the samples analysed, the test method (e.g. infectivity assay, nucleic acid detection), the limit of detection and the limit of quantification. Moreover, since shedding data in human subjects may contribute to/further consolidate the environmental risk assessment of the current dossier, the notifier could be asked whether the study has revealed some data as this information could.

Additional SBB comment

On p 22/27, 2021-003567-10_Annex II ChAd155-hli-HBV (August 2021), section VII.D, the notifier states that 'Since no shedding is expected, there is no expected gene transfer to other species than the target host (i.e. patients enrolled in the clinical study), whereas in section III.1.d, the potential of shedding, albeit limited, is not ruled out on the basis of shedding studies conducted by IM administration of adenoviral vectors.
For consistency reasons, the notifier is requested to correct/adapt the wording along the documents as appropriate.

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

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

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

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Part ChAd155-hli-HBV:

Has evaluated this item and has no questions/comments.

Part MVA-HBV:

P40 “Because it is an epichromosomal virus, the GMO is not capable of gene transfer to the host cell genome.” The expert wonders whether this is always true. The GMO might come into contact with other viruses in the patient receiving the vaccine.

SBB comment

The capacity of gene transfer to the host cell refers to the capacity of integration into the host cell genome, which indeed does not preclude the capacity of MVA derived viral vectors to recombine with other viruses by means of homologous recombination.

Coordinator comment

MVA exhibits a narrow host range and is not able to replicate in human cells. Zoonotic infections are uncommon; chances to get infected with another pox virus are negligible.

Comment 3

Has evaluated this item and has no questions/comments.

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

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Part ChAd155-hli-HBV:

P48. "*The likelihood of post-release selection leading to the expression of unexpected and/or undesirable traits in the modified organism is negligible*."
A possible risk rests on the recombination with an adenovirus present in the test person.

The treated participants in the test do not stay in a hospital but will spread in the environment and will mix with the general population. It might be useful to monitor persons in close contact to the treated patients not only clinically but also with immunological test specific for the vaccine.

SBB comment

Proposed biosafety measures aim at minimizing the probability of health care personnel and/or close contacts to be exposed to possibly shed particles and might be considered proportionate to the risk posed given the replication-deficient properties of ChAd155-hli-HBV and the low probability of shedding.

Monitoring, by immunological testing, is likely to be an approach that is not sensitive and robust enough to assess whether health care personnel and/or close contacts have been exposed to the replication-deficient or highly attenuated recombinant viral vectors. It is also questionable whether such monitoring requirement of health care personnel and/or close contacts is proportional to the potential risk associated to the proposed use of the proposed GMOs? Moreover, it would be quite difficult to put such monitoring in place as it should be determined who will be considered as close contacts (e.g. should health care personnel be monitored considering they are supposed to be trained to avoid exposure to the viral vector? only household contacts or broader ?), and at which time point such monitoring should take place?

Coordinator comment

Agrees with SBB comment

Part MVA-HBV:
P 45 The most important check on an environmental impact might consist of immunological test on close contacts (family members) of the treated patients

SBB comment

See previous SBB comment

Comment 3

Annex IIIA_ P 41 the applicant claims that the GMO is not expected to be pathogenic in immunocompetent or immunocompromised humans since the encoded transgene is not pathogenic. However, infections of immunocompromised persons with adenoviruses can induce severe diseases. What about infection of these persons with the ChAd155 derived vector?

SBB comment

The notifier's claim that '*the GMO is not expected to be pathogenic in immunocompetent or immunocompromised humans since the encoded transgene is not pathogenic*' was also found incorrect or at least insufficiently worked out by the BAC in the context of context of biosafety dossier B/BE/18/BVW4. However, during the evaluation of biosafety dossier B/BE/18/BVW4, one expert of the BAC also remarked that due to the properties of the engineered replication-defective simian-derived adenoviral backbone, the establishment of a propagative infection both in immunocompetent and immunocompromised humans could be prevailed, which is an important argument, next to the transgene(s) not being pathogenic, to expect the ChAd155 not to be non-pathogenic.

The notifier could be suggested to adapt '2021-003567-10_Annex IIIA_ChAd155-hli-HBV (August-2021)' like it was agreed upon for the document ' 2017-001452-55(BBE18BVW4)_th_HBV_ChAd155-HBV_Annex IIIA_ChAd155-hli-HBV (Sep-2018)', which the notifier amended in accordance with the BAC's remarks.

ChAd155 belongs to the subgroup type C of adenoviruses. As a subgroup type C adenovirus that utilizes the coxsackievirus and adenovirus receptor (CAR) to effect entry into host cells, the parental ChAd155 virus isolate could theoretically infect humans.

Risks of recombination events between ChAd155 and other adenoviruses belonging to the same subgroup C and infecting the same host cell, is poorly discussed by the applicant. In particular, such a homologous recombination event could theoretically occur with the human adenovirus serotype 5 which belongs to the same subgroup C, enters the host cell using same receptors and is a commonly circulating virus in our population. The applicant is invited to discuss the probability of such recombination events to occur, possible new forming chimeric adenoviruses and the consequences for human and animal health.

SBB comment

The information on p 11/59 of 2021-003567-10_Annex IIIA_ChAd155-hli-HBV and on p22/27 of 2021-003567-10_Annex II_ChAd155-hli-HBV (August 2021) addressing the potential of generating replication-competent adenoviruses (RCA) during manufacturing may provide some insights on the potential of recombination :

- E1 and E4 regions are deleted in the ChAd155 vector and replaced by the insertion of the E4 region open reading frame 6 (E4orf6) from human adenovirus type 5.
- ChAd155 bears a sequence with high homology with a common circulating human adenovirus of serotype C
- According to the notifier, the lack of sequence homology between the E1 flanking regions of human Ad5 and chimpanzee adenovirus E1 is considered sufficiently low to ensure low levels of RCA

Also, the information on p17/27 of 2021-003567-10_Annex IIIA_ChAd155-hli-HBV (August 2021) addresses, though poorly, the in vivo potential of homologous recombination (for example upon administration of ChAd155 to a subject) between the ChAd155 viral vector and the human Ad5 E1 region. The notifier estimates the probability to be very low due to the lack of sequence homology between the human E1 flanking regions of human Ad5 and chimpanzee adenovirus E1.

Of note, a thorough evaluation was conducted by the BAC on the potential of recombination of another simian adenovirus (ChAdY25 or ChAdOx1) belonging to serotype E that is deleted for E1 and E3, and

which harbors the E4 region of hAd5 (advice of the BAC on dossier B/BE/20/BVW2, issued on 5 June 2020, ref SC/1510/BAC/2020_0511, opinion of the BAC on EMA-dossier EMEA/H/C/005675, ref SC/1510/BAC/2021_0015). It was concluded by the BAC that recombination events with this recombinant simian adenovirus, if it occurs, would likely not lead to any additional environmental risk as compared to circulating wild-type hAd5 adenoviruses.

Notwithstanding the BAC has built some experience with the assessment of recombination with other recombinant replication deficient simian adenoviruses throughout recent biosafety dossiers, the notifier could be requested to elaborate more thoroughly on the probability of occurrence and the outcome of potential recombination events, should it occur.

Coordinator comment

Also in the dossier with respect to the absence of replication competent adenovirus (RCA): The risk of occurrence of the formation of RCA from homologous recombination between the ChAd155 viral vector and the human Ad5 E1 region of the host cell is considered very low, due to the lack of sequence homology between the human E1 flanking regions of human Ad5 and chimpanzee adenovirus E1. It has been shown that recombination and production of RCA does not occur when they are propagated in HEK-293 cells (Colloca et al. 2012), thus eliminating the problem of RCA generation during the adenovector manufacture.
Furthermore in The notification B/BE/18/BVW9 with ChAd155 and ChAd155-RSV it was mentioned that "With respect to the probability for recombination with wild-type adenovirus, the BAC acknowledges Wold and Toth, 2013 concluding that recombination events between replication-deficient adenoviral vectors have not been reported and if these were to occur, these would not lead to replication-competent viruses expressing the transgene.

So, is it necessary to repeat this question, as this question has been asked on similar dossiers several times to the same company (GSK)?
The reasoning above will be reflected in the BAC's advice on the current notification.

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

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

<u>Part ChAd155-hli-HBV and Part MVA-HBV:</u>

Has evaluated this item and has no questions/comments.

Comment 3

Has evaluated this item and has no questions/comments.

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

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Has evaluated this item and has no questions/comments.

Comment 3

Has evaluated this item and has no questions/comments.

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

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Part ChAd155-hli-HBV:

The risk stems from recombination with adenoviruses present in vaccinated persons.

SBB comment

An evaluation of the potential consequences of recombination with adenoviruses is covered in section III.1.c. and IV.1.c. of Annex IIA_ChAd155-hli-HBV (August 2021). See also a related comment in section 5.2. comment 3 and the associated SBB comment.

Part MVA-HBV :

This might occur through a recombination with a virus present in the person who received the vaccine.

Coordinator comment

Chances to get infected with another Vaccinia virus extremely rare – see above

Comment 3 (**Leunda**)

Has evaluated this item and has no questions/comments.

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

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Part ChAd155-hli-HBVand Part MVA-HBV :

Has evaluated this item and has no questions/comments.

Comment 3

See comment in 5.2

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

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Part ChAd155-hli-HBV and Part MVA-HBV :

Has evaluated this item and has no questions/comments.

Comment 3

Has evaluated this item and has no questions/comments.

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

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

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

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Part ChAd155-hli-HBV and Part MVA-HBV :

Has evaluated this item and has no questions/comments.

Comment 3

Has not evaluated this item.

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

Comment 1

See comment in section 4.

Comment 2

Part ChAd155-hli-HBV and Part MVA-HBV :

Has evaluated this item and has no questions/comments.

Comment 3

See comment on use of disinfectants in point 4.

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

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Part ChAd155-hli-HBV and Part MVA-HBV:

The expert does not understand what is meant by "Upon reconciliation and accountability"

SBB comment

The expert's comment relates to p44 of Annex IIA_ChAd155-hli-HBV (August 2021) addressing the techniques foreseen for elimination or inactivation of GMOs at the end of the experiment. In SBB's understanding, 'Upon reconciliation and accountability" refer to the actual amount of viral vectors administered to the patient, which may be lower than what the protocol foresees due to the possible emergence of adverse effects, that need to be reported prior elimination of inactivation of the GMOs.

Part MVA-HBV
Has evaluated this item and has no questions/comments.

Comment 3

Has evaluated this item and has no questions/comments.

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

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Part ChAd155-hli-HBV and Part MVA-HBV:

Has evaluated this item and has no questions/comments.

Comment 3

The applicant is asked to precise which disinfectant should be used in case of an accidental spill with the ChAd155 based vector.
A written spill management procedure can be provided by the applicant to clinical centres. It is important that this procedure takes into consideration aerosols generated by spillage and time for their sedimentation (30 minutes are generally required) as well as protection equipment to be worn by implicated personnel (gloves, gown, mask and goggles).

SBB comment

With respect to the comment on the type of disinfectant, we refer to the comments raised in section 4 comment 1 and comment 3

With respect to the generation of aerosols, a similar question was raised by the BAC in the context of dossier B/BE/18/BVW4. The notifier could therefore be reminded to the additional biosafety instructions that were described, upon request of the BAC, for steps potentially leading to the generation of aerosols in the document 2017-001452-55 (BBE18BVW4)-Biosafety instructions for site staff (version 28 Aug2018). The notifier could be requested to adapt the Biosafety instructions for site staff associated to the current biosafety dossier and add the following : '*In addition during the steps that may lead to the creation of aerosols (piercing of the vaccine rubber, air expelling from the needle) site staff is also recommended to wear safety glasses and facial mask*'.

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

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Part ChAd155-hli-HBV and Part MVA-HBV:

Has evaluated this item and has no questions/comments.

Comment 3

Has not evaluated this item

7. OTHER INFORMATION

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

Comment 1

The document '2021-003567-10_Annex IIIA_ChAd155-hli-HBV (August 2021)' mentions on page 18 of 59 under the item 'Parental organism' that adenoviruses are susceptible to heat and disinfectants active against enveloped viruses. This is not correct since adenoviruses are non-enveloped and consequently disinfectants against enveloped viruses are not always also effective against non-enveloped viruses.

SBB comment

This comment is in line with the one raised under section 4 , comment 3 . See also related SBB comment.

Comment 2

Part ChAd155-hli-HBV and Part MVA-HBV:

As so often with this type of dossier the applicant tends to under-evaluate possible risks linked to the introduction of a technology that very likely is in the general interest. It is however important for the credibility of the scientific approach not to deny the existence of possible risks

Comment 3

In 2021-003567-10_Annex IIIA_ChAd155-hli-HBV (August 2021) p16-17, (b) Recipient and (c) Parental : an error seems to have occurred in the text: "The presence of RCA is assessed on the master virus seed MVA…" However, this is the annex on the ChAd155-hli-HBV vaccine

SBB comment

This comment could be forwarded to the notifier as '*typos and/or editorial remarks*' .

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