1. *Identification of characteristics which may cause adverse effects:*

Any characteristics of the GMOs linked to the genetic modification that may result in adverse effects on human health or the environment shall be identified. A comparison of the characteristics of the GMO(s) with those of the non-modified organism under corresponding conditions of the release or use, will assist in identifying the particular potential adverse effects arising from the genetic modification. It is important not to discount any potential adverse effect on the basis that it is unlikely to occur.

Potential adverse effects of GMOs will vary from case to case, and may include:

- disease to humans including allergenic or toxic effects (see e.g. items IIA(11) and IIC(2)(i) in Annex IIIA, and B(7) in Annex IIIB);

- disease to animals and plants including toxic, and where appropriate, allergenic effects (see e.g. items IIA(11) and IIC(2)(i) in Annex IIIA, and B(7) and D(8) in Annex IIIB);

Neither wild type AAV nor the experimental vector AVXS-101 is known to be pathogenic to humans. AVXS-101 is a recombinant biological product that is comprised of a non-replicating, non-integrating recombinant self-complementary adeno-associated virus serotype 9 (AAV9) capsid shell containing the cDNA of the human SMN gene under the control of the cytomegalovirus (CMV) enhancer/chicken-β-actin-hybrid promoter (CB) as well as two AAV inverted terminal repeats (ITR) from the AAV serotype 2 (AAV2) DNA. The left AAV ITR has been modified to promote intramolecular annealing of the transgene, thus forming a double-stranded transgene ready for transcription. This modified ITR, termed a "self-complementary" (sc) ITR, has been shown to significantly increase the speed at which the transgene is transcribed and the resulting human SMN protein is produced. Recombinant scAAV can be employed for AVXS-101 because of the small size of the SMN gene, which enables efficient packaging and allows for efficient gene transfer with lower viral titers, compared with prototypical single-stranded AAV vectors. All of the DNA from the wild-type AAV9 has been removed and replaced with the genes described above (the two ITRs are from AAV2). These modifications render AVXS-101 incapable of replicating itself which may be considered a potential safety benefit, when compared to integrating vectors with the ability to replicate, in that the total dose of virus administered to a patient can be carefully controlled and there is minimal risk of unintended transmission. AVXS-101 is dosed as a one-time intravenous infusion.

AVXS-101 does not contain any of the viral genes necessary for replication (rep, cap) and thus is replication defective even in the presence of a helper virus. Only in the hypothetical situation that a cell is co-infected with AVXS-101, wild type AAV, and helper virus, replication of

(disseminated) AVXS-101 could occur. Thus, the pathogenicity of AVXS-101 is expected to be even less than that of its parental AAV2 or AAV9 viruses, which are already considered non-pathogenic.

Wild type AAV is not classified in Risk Groups 2,3, or 4 in the European Union (EU) according to directive 2000/54/EC on protection of workers from risks related to exposure to biological agents at work (Appendix III). It is most appropriately designated a Risk Group 1 biological agent, defined in the EU as 'one that is unlikely to cause human disease'. All of the DNA from the wild-type AAV9 has been removed and replaced with the genes described below (the two ITRs are from AAV2). These modifications render AVXS-101 incapable of replicating itself which may be considered a potential safety benefit, when compared to integrating vectors with the ability to replicate, in that the total dose of virus administered to a patient can be carefully controlled and there is minimal risk of unintended transmission. The only viral sequences included in the vector construct for AVXS-101 are the ITRs of AAV2, which are required for both viral DNA replication and the packaging of the rAAV vector genome. This makes AVXS-101 unlikely to cause disease in humans.

Similar classifications of hazard have been assigned to wild type AAV according to the definitions of the World Health Organisation (WHO) WHO Laboratory Biosafety Manual 2004, and in the US NIH Recombinant DNA guidelines 2016.

AVXS-101 is a non-replicating vector and the administration of AVXS-101 to patients is associated with limited exposure of the environment to AVXS-101. Thus, exposure of plants or animals is not expected.

AVXS-101 is non-pathogenic and the human SMN protein is not known to have toxic effects. No side-effects have been reported for the environment or human health after the release of similar GMOs (adeno-associated virus from serotypes 2 and 9). AAV2 and AAV9 are non-pathogenic, toxigenic, virulent, allergenic or a carrier (vector) of a pathogen. Vector shedding can be found in the urine, saliva, and stool for up to a few weeks following injection. The risks associated with the shed vector are not known at this time; however, it is unlikely as the vector is non-infectious and cannot replicate. Regardless, instructions should be provided to patient families and care givers regarding use of protective gloves if/when coming into direct contact with patient bodily fluids and/or waste as well as good hand-hygiene for a few weeks after the injection. Additionally, patients are prohibited from donating blood for two years following the vector injection.

Based on 20 Jan 2017 data from the Phase 1 study AVXS-101-CL-101, AVXS-101 appears to be safe and well tolerated when administered to infants with SMA, and has demonstrated encouraging early evidence of clinically meaningful efficacy in this otherwise devastating neurodegenerative disease. AVXS-101 administration in the AVXS-101-CL-101 study has resulted in marked and positive impact on motor function and motor milestone achievement.

As of 20 Jan 2017, mean increases from baseline in CHOP-INTEND scores of 7.7 points in Cohort 1 and 24.7 points in Cohort 2 were observed, reflecting a substantial improvement in motor function relative to the natural history of Type 1 SMA. All patients in both dosing cohorts experienced a sustained increase in CHOP-INTEND scores above baseline; in Cohort 2, 11 of 12 patients achieved CHOP-INTEND scores greater than or equal to 40. Many patients in Cohort 2 have achieved and sustained motor milestones (such as sitting unassisted) which are not achieved in the natural history of Type 1 SMA as described in recent published natural history studies. Given the devastating clinical course of Type 1 SMA, the irreversible and progressive nature of motor neuron loss as the disease progresses, and the urgent and substantial unmet medical need in this serious disorder, the available data strongly support a positive benefit/risk relationship and strongly support continued study of AVXS-101 in patients with SMA.

In the most recent cut-off data (7 August 2017), AVXS-101 continues to show a favorable safety and tolerability profile and further improvement in efficacy. As of 7 August 2017, patients treated with AVXS-101 continue to demonstrate improved nutritional status including lower instances of feeding support (e.g., G-tube, NJ tube), improvement in motor function and achievement of developmental milestones such as sitting unassisted. Key efficacy findings related to motor function (when all treated patients reached 20 months of age or older post gene therapy) and safety data description can be found in the article by Mendell et al., 2017.

Because of the limited number of patients treated with AVXS-101 to date, the potential risks associated with AVXS-101 are not fully known at this time. Patients could develop an immune response to the AAV9 viral vector, which could interfere with or prevent future use of gene transfer interventions using this vector. Elevated liver function tests have been observed in the ongoing AVXS-101-CL-101 trial, which is believed to reflect a T-cell immune response to the AAV9 vector. None of the liver enzyme abnormalities observed in the trial were accompanied by clinical sequelae, and all have resolved following treatment with prednisolone. Although no other treatment-related AEs have been reported to date, other potential risks of treatment may exist that are not currently known given the limited clinical experience to date, and the benefit/risk profile will continue to become better characterized with continued study.

Nonclinical data in nonhuman primates and mouse models of SMA provide additional support for a positive benefit/risk relationship, and support continued clinical investigation of AVXS-101 in patients with SMA. Some mice affected with a form of SMA Type 1 that were treated with the study vector developed localized vascular necrosis around the ear called necrotic pinna. This is believed to be unrelated to the vector, and likely related to an underlying defect that has been observed to occur in several SMA mouse models (Narver et al. 2008). The relevance to humans with spinal muscular atrophy is unknown.

Some mice affected with SMA Type 1 that were treated with AVXS-101 experienced changes in liver function enzymes and also tiny deterioration and repair of tissues in the heart and liver; the heart and liver changes were visible only by a microscope. AVXS-101 will likely express SMN protein in many different cell types in addition to motor neurons. While expression of SMN protein in many different cell types is not currently associated with any negative impact, all consequences are not known at this time.

Taken together, results from the clinical and nonclinical studies to date support continued clinical investigation of the efficacy and safety of AVXS-101 in patients with SMA Type 1, and additionally support further investigation of intravenous and intrathecal administration of AVXS-101 in a broader population of patients with SMA.

The effects of unintended exposure of human beings to AVXS-101 are the same as those from intended exposure to subjects (patients): effects related to the expression SMN protein, induction of anti-AAV9 immune responses, and potential consequences of insertional mutagenesis and vertical transmission. The likelihood that these effects occur and/or cause harmful effects are negligible, because unintended exposure of human beings to (infectious) AVXS-101 can only be many orders of magnitude lower than the subjects' exposure due to the replications incompetence of AVXS-101 and the limited amount and duration (if any) of infections AVXS-101 shedding from subjects. Neither wild type AAV nor the experimental vector AVXS-101 is known to be pathogenic to humans. The administration of an AAV vector has the risk of causing immune-mediated hepatitis. For patients who have positive serology for hepatitis B or C, administration of AAV vector may represent an unreasonable risk; therefore, negative serology testing must be confirmed prior to treatment.

- effects on the dynamics of populations of species in the receiving environment and the genetic diversity of each of these populations (see e.g. items IVB(8), (9) and (12) in Annex IIIA);

Dissemination of AVXS-101 would most likely only occur between human beings, since it is derived from AAV2/9. However, no replication is expected in normal cells of treated individuals exposed to the replication-deficient virus, or from exposure of uninfected people to treated individuals.

AVXS-101 is a replication-incompetent virus derived from AAV2/9 and is therefore at a competitive disadvantage when compared to its parent strain / wild type AAV. The transgene (human survivor motor neuron) is not expected to confer any advantage to the GMO in terms of survival and selective pressure.

AVXS-101 is derived from the non-pathogenic AAV2/9. AVXS-101 is non-replicative by deletion of the rep and cap genes rendering it unable to replicate, even in the presence of a helper virus. Therefore, infection leading to replication of the GMO (and therefore potential for dispersal) is not possible under normal circumstances. AAV shows some species specificity but can replicate in cells of a different species when infected with AAV in vitro, provided it is in the presence of a

helper virus to which that species is permissive. It is not known whether zoonosis occurs in nature, nor whether other species can act as carriers or vectors under natural conditions. However, given the inability to replicate and site of administration, the possibility of exposure of AVXS-101 to non-humans is considered negligible.

The non-target organisms which could conceivably be affected are unintended human recipients (healthcare workers and close contacts of the patient). It is not expected that transmission would lead to adverse effects in healthy humans since neither wild type AAV nor AVXS-101 are known to be pathogenic. In the unlikely event that transmission to a healthy unintended human recipient occurs it is likely that the safety profile in healthy subjects would be at worst similar to those expected in patients.

- altered susceptibility to pathogens facilitating the dissemination of infectious diseases and/or creating new reservoirs or vectors;

- compromising prophylactic or therapeutic medical, veterinary, or plant protection treatments, e.g. by transfer of genes conferring resistance to antibiotics used in human or veterinary medicine (see e.g. items IIA(11) e) and IIC((2)(i)(iv) in Annex IIIA);

Antibiotics are not effective in the treatment of viral infection, nor does wild type AAV present specific resistance to antibiotics. The wild type virus does not contain any gene that confers resistance to known antibiotics.

Neither wild type AAV nor the experimental vector AVXS-101 is known to be pathogenic to humans. The administration of an AAV vector has the risk of causing immune-mediated hepatitis. For patients who have positive serology for hepatitis B or C, administration of AAV vector may represent an unreasonable risk; therefore, negative serology testing must be confirmed prior to treatment.

- effects on biogeochemistry(biogeochemical cycles), particularly carbon and nitrogen recycling through changes in soil decomposition of organic material (see e.g. items IIA(11) f) and IVB(15) in Annex IIIA, and D(11) in Annex IIIB).

Wild type AAV is not known to be involved in environmental processes. It does not respire and does not contribute to primary production or decomposition processes. In its virion form, it does not display any metabolic activity. There is no known or predicted involvement in biogeochemical processes.

Adverse effects may occur directly or indirectly through mechanisms which may include:

- the spread of the GMO(s) in the environment

- the transfer of the inserted genetic material to other organisms, or the same organism whether genetically modified or not

- phenotypic and genetic instability

- interactions with other organisms

- changes in management, including, where applicable, in agricultural practices.

Potential adverse effects	AVXS-101
the spread of the GMO(s) in the environment	*There are three potential scenarios in which AVXS-101 may disperse from patients into the environment: via needle stick injury during IMP administration, via blood following needle stick injury or via shedding directly from the patient. Routes of the virus dispersing from the test subject into the environment are via bodily fluids such as urine, stool, blood and saliva.*
the transfer of the inserted genetic material to other organisms, or the same organism whether genetically modified or not	*AVXS-101 is derived from the non-pathogenic AAV2/9. AVXS-101 is non-replicative by deletion of the rep and cap genes rendering it unable to replicate, even in the presence of a helper virus. Therefore, infection leading to replication of the GMO (and therefore potential for dispersal) is not possible under normal circumstances. AAV shows some species specificity but can replicate in cells of a different species when infected with AAV in vitro, provided it is in the presence of a helper virus to which that species is permissive. It is not known whether zoonosis occurs in nature, nor whether other species can act as carriers or vectors under natural conditions. However, given the inability to replicate and site of administration, the possibility of exposure of AVXS-101 to non-humans is considered negligible. In the unlikely event that transmission to a healthy unintended human recipient occurs it is likely that the safety profile in healthy subjects would be at worst similar to that expected in patients*
phenotypic and genetic instability	*AVXS-101 is expected to be genetically stable. In general, DNA viruses have greater genetic stability than RNA viruses. Evolution of AAV viruses (like all viruses) is directed by spontaneous mutation or homologous recombination with other viruses of the same species, where such genetic modification confers a selective advantage. Homologous genomic recombination may occur spontaneously in nature between the viral genomes of AAV strains only under circumstances where a cell of the host organism is infected simultaneously by two different strains of AAV and a helper virus which is permissive in that species (triple-infection). In the case of AVXS-101, such recombination could only result in*

	the exchange of the hSMN expression cassette with the rep and cap genes of the wild type virus. It is not possible for the AAV genome to contain both rep/cap genes and the transgene, as this is beyond the packaging limit of the virion. Therefore, the only mechanism by which the transgene could be mobilized is through a triple infection of the same cell by AVXS-101 (containing the transgene), wild type AAV (providing the rep and cap functions) and a helper virus. This scenario is expected to be a rare event, and would only result in the production of more wild type AAV and more AVXS-101 vector particles (which would still lack rep and cap genes and consequently could not be self-sustaining). *Long-term transgene expression after dosing with AVXS-101 has been demonstrated in mice over 365 days and in non-human primates for at least 18 months with no signs of diminished durability.*
interactions with other organisms	*AAV shows some species specificity, but can replicate in cells of a different species when infected with AAV in vitro, provided it is in the presence of a helper virus to which that species is permissive. It is not known whether zoonosis occurs in nature, nor whether other species can act as carriers or vectors under natural conditions. However, given the inability to replicate and site of administration, the possibility of exposure of AVXS-101 to non-humans is considered negligible.*
changes in management, including, where applicable, in agricultural practices	*None known*

2. *Evaluation of the potential consequences of each adverse effect, if it occurs*

The magnitude of the consequences of each potential adverse effect should be evaluated.

This evaluation should assume that such an adverse effect will occur. The magnitude of the consequences is likely to be influenced by the environment into which the GMO(s) is (are) intended to be released and the manner of the release.

Potential adverse effects	AVXS-101	Magnitude of the consequence

the spread of the GMO(s) in the environment	*-via needle stick injury during IMP administration,* *via blood following needle stick injury or* *via shedding directly from the patient.*	*Given the low number of patients expected to be exposed since SMA is a rare disease, and the level of expertise and training of the medical personnel allowed to manipulate the IMP, and to obtain patient samples, it is very unlikely that the GMO will spread from the test subject into the environment as the levels of the GMO in the blood of the treated patient are barely detectable and the route of administration poses a negligible risk of shedding from patients. The infectivity risk is low as AVXS-101 is a non-replicating recombinant adeno-associated virus.*
the transfer of the inserted genetic material to other organisms, or the same organism whether genetically modified or not	*AVXS-101 is derived from the non-pathogenic AAV2/9. AVXS-101 is non-replicative by deletion of the rep and cap genes rendering it unable to replicate, even in the presence of a helper virus.*	*Infection leading to replication of the GMO (and therefore potential for dispersal) is not possible under normal circumstances. AAV shows some species specificity, but can replicate in cells of a different species when infected with AAV in vitro, provided it is in the presence of a helper virus to which that species is permissive. It is not known whether zoonosis occurs in nature, nor whether other species can act as carriers or vectors under natural conditions. However, given the inability to replicate and site of administration, the possibility of exposure of AVXS-101 to non-humans is considered negligible. In the unlikely event that transmission to a healthy unintended human recipient occurs it is likely that the safety profile in healthy subjects would be at worst similar to that expected in patients*

phenotypic and genetic instability	*AVXS-101 is expected to be genetically stable.*	*In general, DNA viruses have greater genetic stability than RNA viruses. Evolution of AAV viruses (like all viruses) is directed by spontaneous mutation or homologous recombination with other viruses of the same species, where such genetic modification confers a selective advantage. Homologous genomic recombination may occur spontaneously in nature between the viral genomes of AAV strains only under circumstances where a cell of the host organism is infected simultaneously by two different strains of AAV and a helper virus which is permissive in that species (triple-infection). In the case of AVXS-101, such recombination could only result in the exchange of the hSMN expression cassette with the rep and cap genes of the wild type virus. It is not possible for the AAV genome to contain both rep/cap genes and the transgene, as this is beyond the packaging limit of the virion. Therefore, the only mechanism by which the transgene could be mobilized is through a triple infection of the same cell by AVXS-101 (containing the transgene), wild type AAV (providing the rep and cap functions) and a helper virus such as rhinoviruses, adenovirus, or herpes.* *This scenario is expected to be a rare event, and would only result in the production of more wild type AAV and more AVXS-101 vector particles (which would still lack rep and cap genes and*

		consequently could not be self-sustaining). The rescue, replication and packaging would stop; however, as the helper viruses, such as rhinoviruses, adenovirus, or herpes were cleared by the patient's immune system.
interactions with other organisms	*AAV shows some species specificity and is primarily detected in humans,*	*AAV can replicate in cells of a different species when infected with AAV in vitro, provided it is in the presence of a helper virus to which that species is permissive. It is not known whether zoonosis occurs in nature, nor whether other species can act as carriers or vectors under natural conditions. However, given the inability to replicate and site of administration, the possibility of exposure of AVXS-101 to non-humans is considered negligible.*
changes in management, including, where applicable, in agricultural practices	*None known*	

3. *Evaluation of the likelihood of the occurrence of each identified potential adverse effect*

A major factor in evaluating the likelihood or probability of adverse effects occurring is the characteristics of the environment into which the GMO(s) is intended to be released, and the manner of the release.

Potential adverse effects	AVXS-101	Likelihood of occurrence
the spread of the GMO(s) in the environment	*-via needle stick injury during IMP administration,* *via blood following needle stick injury or*	*Given the low number of patients expected to be exposed since SMA is a rare disease, and the level of expertise and training of the medical personnel allowed to manipulate the IMP, and to obtain patient samples, it is very*

	via shedding directly from the patient.	*unlikely that the GMO will spread from the test subject into the environment as the levels of the GMO in the blood of the treated patient are barely detectable and the route of administration poses a negligible risk of shedding from patients. The infectivity risk is low as AVXS-101 is a non-replicating recombinant adeno-associated virus.*
the transfer of the inserted genetic material to other organisms, or the same organism whether genetically modified or not	*AVXS-101 is derived from the non-pathogenic AAV2/9. AVXS-101 is non-replicative by deletion of the rep and cap genes rendering it unable to replicate, even in the presence of a helper virus.*	*Given the inability of AVXS-101 to replicate and administration in a hospital setting, the possibility of exposure of AVXS-101 to non-humans is considered negligible.*
phenotypic and genetic instability	*AVXS-101 is expected to be genetically stable.*	*The only mechanism by which the transgene could be mobilized is through a triple infection of the same cell by AVXS-101 (containing the transgene), wild type AAV (providing the rep and cap functions) and a helper virus. This scenario is expected to be a rare event, and would only result in the production of more wild type AAV and more AVXS-101 vector particles (which would still lack rep and cap genes and consequently could not be self-sustaining).*
interactions with other organisms	*AAV shows some species specificity and is primarily detected in humans,*	*Given the inability to replicate and site of administration, the possibility of exposure of AVXS-101 to non-humans is considered negligible.*
changes in management, including, where applicable, in agricultural practices	*None known*	*None known*

4. *Estimation of the risk posed by each identified characteristic of the GMO(s)*

An estimation of the risk to human health or the environment posed by each identified characteristic of the GMO which has the potential to cause adverse effects should be made as far as possible, given the state of the art, by combining the likelihood of the adverse effect occurring and the magnitude of the consequences, if it occurs.

SMA is a rare disease and therefore the number of test subjects in AVXS-101-CL-304 study is low, up to 44 patients globally. The number of patients expected to be administered therapy if the test results are positive is expected to be approx. 500 patients per year in Europe. Adverse effects of AAV9 infection are typically not clinically significant. The slightly larger risk would be if two siblings were candidates for therapy and they were administered therapy at different times. One sibling could possibly be exposed to AAV9 and develop neutralizing antibodies to the therapy prior to administration.

For each of the risks listed in section 4 the risk to human health or the environment is very low. AVXS-101 will be administered to the patient by a medical professional in a medical facility. The product itself will be stored prior to administration in a secure environment (pharmacy). AVXS-101 is non-pathogenic wild-type AAV2/9, modified by deletion of the rep and cap genes rendering it unable to replicate, even in the presence of a helper virus. As a derivative of primate (human) AAV2/9, the primary indigenous vector of AVXS-101 is human beings. The non-target organisms which could conceivably be affected are unintended human recipients (healthcare workers and close contacts of the patient). It is not expected that transmission would lead to adverse effects in healthy humans since neither wild type AAV nor AVXS-101 are known to be pathogenic. In the unlikely event that transmission to a healthy unintended human recipient occurs it is likely that the safety profile in healthy subjects would be at worst similar to those expected in patients.

Given the nature of the product administration (intravenous), and the transient/ low levels of shedding expected, the risk of unintended exposure to AVXS-101 to humans and other biota is minimal.

5. *Application of management strategies for risks from the deliberate release or marketing of GMO(s)*

The risk assessment may identify risks that require management and how best to manage them, and a risk management strategy should be defined.

Patients will receive a one-time dose of AVXS-101 via intravenous (IV) infusion. AVXS-101 drug product is supplied in clear, single-use, sterile vials. The clinical site pharmacist will prepare the AVXS-101 product under sterile conditions; a Class II BSC is recommended, for sterility, but not required. The total vector genome (vg) dose will be calculated based on patient's body weight. The appropriate number and size of vials will be determined for each patient based on body weight. All transfers of AVXS-101 must be done in spill-proof containers. Individuals manipulating the vector will be required to wear personal protective equipment. The empty vial and syringes used for delivery of the vector should be sealed in bags bearing the biohazard symbol and returned to AveXis unless prevented by the research site's SOPs.

The AVXS-101 intravenous infusion procedure should be performed under sterile conditions in a PICU patient room or other appropriate setting (e.g., interventional suite, operating room, dedicated procedure room) with immediate access to acute critical care management. AVXS-101 will be delivered one-time through a venous catheter inserted into a peripheral limb vein (arm or leg) and slowly infused over approximately 30 -60 minutes.

Following administration, patients should return to an appropriate designated post-operative or pediatric intensive care unit to ensure close monitoring of vital signs and adverse reactions. Vitals should be monitored every 15 minutes for four hours and every hour for 24 hours. Patients may be discharged 24 hours after the infusion, based on Investigator judgment.

Blood and urine samples will be collected at scheduled . Internal transport of the samples within the investigational site should be done in spill-proof containers. Samples for laboratory tests required during the in-patient vector infusion period prior to dosing will be collected and processed by the investigative site's local laboratory.

Safety measures for biosafety level 1 agents will be utilized. Additionally: Preparation AVXS-101 should be completed in accord with local/national aseptic techniques. The clinical site pharmacist will prepare the AVXS-101 vector product under sterile conditions. Protective laboratory coats, gowns, or uniforms are recommended to prevent contamination of personal clothing. Wear protective eyewear when conducting procedures that have the potential to create splashes of microorganisms or other hazardous materials. Persons who wear contact lenses in laboratories should also wear eye protection. Gloves must be worn to protect hands from exposure to hazardous materials. Glove selection should be based on an appropriate risk assessment. Alternatives to latex gloves should be available. Wash hands prior to leaving the laboratory. All materials used for injection, including sterile drapes, needles, and syringes in contact with the vector must be sealed in leak-proof primary and secondary containers. All waste must be double bagged in bags bearing the biohazard symbol. The bag must then be disposed of in a biohazard waste container.

AVXS-101 is non-pathogenic and the human SMN protein is not known to have toxic effects. No side-effects have been reported for the environment or human health after the release of similar GMOs (adeno-associated virus from serotypes 2 and 9). Vector shedding can be found in the blood, urine, saliva, and stool for up to a few weeks following injection. The risks associated with the shed vector are not known at this time; however, it is unlikely as the vector is non-infectious and cannot replicate. Regardless, instructions should be provided to patient families

and care givers regarding use of protective gloves if/when coming into direct contact with patient bodily fluids and/or waste as well as good hand-hygiene for a few weeks after the injection. Additionally, patients are prohibited from donating blood for two years following the vector injection.

6. *Determination of the overall risk of the GMO(s)*

An evaluation of the overall risk of the GMO(s) should be made taking into account any risk management strategies which are proposed.

AVXS-101 is non-pathogenic and the human SMN protein is not known to have toxic effects. No side-effects have been reported for the environment or human health after the release of similar GMOs (adeno-associated virus from serotypes 2 and 9). Vector shedding can be found in the blood, urine, saliva, and stool for up to a few weeks following injection. The risks associated with the shed vector are not known at this time; however, it is unlikely as the vector is non-infectious and cannot replicate. Regardless, instructions should be provided to patient families and care givers regarding use of protective gloves if/when coming into direct contact with patient bodily fluids and/or waste as well as good hand-hygiene for a few weeks after the injection. Additionally, patients are prohibited from donating blood for two years following the vector injection.

D. **Conclusions on the potential environmental impact from the release or the placing on the market of GMOs**

On the basis of an e.r.a. carried out in accordance with the principles and methodology outlined in sections B and C, information on the points listed in sections D1 or D2 should be included, as appropriate, in notifications with a view to assisting in drawing conclusions on the potential environmental impact from the release or the placing on the market of GMOs:

D1. In the case of GMOs other than higher plants

1. Likelihood of the GMO to become persistent and invasive in natural habitats under the conditions of the proposed release(s).

AVXS-101 is a non-replicating vector; therefore, it is not possible that it becomes persistent and invasive in natural habitats.

2. Any selective advantage or disadvantage conferred to the GMO and the likelihood of this becoming realised under the conditions of the proposed release(s).

AVXS-101 is at a significant disadvantage to wild-type AAV under the conditions of the release as it is a non-replicating vector and does not persist for a significant length of time outside the patient.

3. Potential for gene transfer to other species under conditions of the proposed release of the GMO and any selective advantage or disadvantage conferred to those species.

AVXS-101 is administered in a controlled environment, where access to non-humans is limited. In addition, vector shedding from subjects is negligible and no selective advantages or disadvantages are conferred over untreated individuals.

4. Potential immediate and/or delayed environmental impact of the direct and indirect interactions between the GMO and target organisms (if applicable)

No interactions between the GMO and non-target organisms are expected given the quantities involved, the nature of the release and the non-replicative nature of AVXS-101.

5. Potential immediate and/or delayed environmental impact of the direct and indirect interactions between the GMO with non-target organisms, including impact on population levels of competitors, prey, hosts, symbionts, predators, parasites and pathogens.

No potential immediate and/or delayed environmental effects of the direct and indirect interactions between the GMO with non-target organisms, including impact on population levels of competitors, prey, hosts, symbionts, predators, parasites and pathogens are expected given the quantities involved, the nature of the release and the non-replicative nature of the GMO.

6. Possible immediate and/or delayed effects on human health resulting from potential direct and indirect interactions of the GMO and persons working with, coming into contact with or in the vicinity of the GMO releases(s).

No interactions between the GMO and persons working with or coming into contact with the GMO are expected given the quantities involved, the nature of the release and the non-replicative nature of the GMO.

7. Possible immediate and/or delayed effects on animal health and consequences for the feed/food chain resulting from consumption of the GMO and any product derived from it if it is intended to be used as animal feed.

No effects on animal health or consequences for the feed/food chain are expected.

8. Possible immediate and/or delayed effects on biogeochemical processes resulting from potential direct and indirect interactions of the GMO and target and non-target organisms in the vicinity of the GMO release(s).

Immediate and/or delayed effects on biogeochemical processes are not expected. As AVXS-101 is a non-replicating vector and the administration of AVXS-101 to patients is associated with limited exposure of the environment to AVXS-101, it is not deemed to have an impact on the biogeochemical processes.

9. Possible immediate and/or delayed, direct and indirect environmental impacts of the specific techniques used for the management of the GMO where these are different from those used for non-GMOs.

Given the low number of patients expected to be exposed since SMA is a rare disease, and the level of expertise and training of the medical personnel allowed to manipulate the IMP, and to obtain patient samples. With the use by patient families, and care givers of protective gloves if/when coming into direct contact with patient bodily fluids and/or waste as well as good hand-hygiene for a few weeks after the injection, it is very unlikely that the GMO will spread from the test subject into the environment as the levels of the GMO in the blood of the treated patient are barely detectable and the route of administration poses a negligible risk of shedding from patients. The infectivity risk is low as AVXS-101 is a non-replicating recombinant adeno-associated virus. Additionally, patients are prohibited from donating blood for two years following the vector injection.

D2. In the case of genetically modified higher plants (GMHP)

Section D2 is not applicable for AVXS-101.

1. Likelihood of the GMHP becoming more persistent than the recipient or parental plants in agricultural habitats or more invasive in natural habitats.

2. Any selective advantage or disadvantage conferred to the GMHP.

3. Potential for gene transfer to the same or other sexually compatible plant species under conditions of planting the GMHP and any selective advantage or disadvantage conferred to those plant species

4. Potential immediate and/or delayed environmental impact resulting from direct and indirect interactions between the GMHP and target organisms, such as predators, parasitoids, and pathogens (if applicable).

5. Possible immediate and/or delayed environmental impact resulting from direct and indirect interactions of the GMHP with non-target organisms, (also taking into account organisms which interact with target organisms), including impact on population levels of competitors, herbivores, symbionts (where applicable), parasites and pathogens.

6. Possible immediate and/or delayed effects on human health resulting from potential direct and indirect interactions of the GMHP and persons working with, coming into contact with or in the vicinity of the GMHP release(s).

7. Possible immediate and/or delayed effects on animal health and consequences for the feed/food chain resulting from consumption of the GMO and any products derived from it if it is intended to be used as animal feed.

8. Possible immediate and/or delayed effects on biogeochemical processes resulting from potential direct and indirect interactions of the GMO and target and non-target organisms in the vicinity of the GMO release(s).

9. Possible immediate and/or delayed, direct and indirect environmental impacts of the specific cultivation, management and harvesting techniques used for the GMHP where these are different from those used for non-GMHPs.