# Information for the Public

(According to Annex VIII.A of the Royal Decree of 21 February 2005)

# AVXS-101

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## 1. Developmental framework

The objective of this clinical development program is to assess the tolerability and efficacy of gene therapy for treatment of Spinal Muscular Atrophy (SMA). The specific purpose of the clinical studies is to assess the safety, tolerability and efficacy of a single dose of AVXS-101 for treatment of SMA.

## 2. Information on AVXS-101

AVXS-101 is a recombinant biological product that is comprised of a non-replicating, non-integrating recombinant self-complementary adeno-associated virus serotype 2/9 (AAV2/9) 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 encodes for the human SMN protein, the loss of which appears to be the root cause of SMA.

Wild-type adeno-associated virus (AAV) is a single-stranded DNA virus with a non-enveloped icosahedral capsid with a diameter of approximately 25nm. The AAV genome is approximately 4.7 kilobase long and comprises inverted terminal repeats (ITRs) at both ends of the DNA strand, and two open reading frames (ORFs), rep and cap. ORF 'rep' is composed of four overlapping genes encoding Rep proteins required for DNA replication, and ORF 'cap' contains overlapping nucleotide sequences coding for capsid proteins (VP1, VP2 and VP3) which interact together to form a capsid of an icosahedral symmetry. The inverted terminal repeats (ITRs) flank the two ORFs and contain all cis-acting functions required for DNA replication, packaging, integration into the host genome, and subsequent excision and rescue.

There are several serotypes of adeno-associated virus. The serotype of AAV is determined by the capsid of the virion, which is integral to the tissue tropism and infection efficiency of AAV.

The virus causes a very mild immune response at doses of exposure in the natural habitat of the human, lending further support to its apparent lack of pathogenicity.

Replication of wild-type AAV is dependent on co-infection of helper viruses such as adenovirus or herpes-simplex virus. In presence of helper virus, AAV undergoes productive infection characterized by genome replication, viral gene expression and virion production. In absence of a

herpes virus co-infection, the virus DNA will persist within infected cells in episomal form or may integrate into the host cell genome. In both cases the virus remains latent.

AAV is a non-enveloped virus that is relatively stable in the environment and stable to desiccation. AAV is sensitive to appropriate viricidal disinfectants, such as 1000 PPM chlorine solution.

## 3. Information on the clinical application of AVXS-101

SMA (all types) is a rare disease with an annual incidence of less than 0.4 in 10,000 people in the European Union (EU28). This is equivalent to a total of fewer than 21,000 people in the European Union, and does not account for the reduced prevalence due to early mortality compared with the general population. The root cause of SMA is the bi-allelic deletion or mutation of the *SMN1* gene resulting in diminished levels of Survival Motor Neuron (SMN) protein, a protein that is critical for motor neuron survival. The *SMN1* gene is the primary producer of SMN protein, a ubiquitously expressed protein that is essential in all tissues and is not associated with toxicity when over-expressed. *SMN2*, a gene closely homologous to *SMN1* produces a limited amount of functional SMN protein that can partially compensate for the loss of *SMN1* function. In addition, disease severity appears to correlate with SMN protein levels emphasizing the potential therapeutic benefit for increasing SMN as a treatment strategy in the disease. Intervention at a very early age before motor neurons are irretrievably lost is likely to yield the most benefit for patients. The diagnosis of SMA is based on the combination of the onset of clinical symptoms and genetic testing confirming both the deletion/loss of function of *SMN1* genes and determining the number of copies of the *SMN2* backup gene. In general, the number of copies of the *SMN2* backup gene is also predictive of the severity of the phenotype; the more copies of the *SMN2* gene, the less severe the disease in general. *SMN2* generally produces between 10–20% of fully functioning SMN protein compared to the primary *SMN1* gene due to a splicing defect that largely excludes exon 7.

The classification of spinal muscular atrophy or SMA is shown below (Table 1) in which SMA Types 0 to 4 are described. SMA is conventionally classified into 4 phenotypes on the basis of age at onset and highest motor function achieved, with an additional phenotype (Type 0) to describe the severe forms of antenatal-onset SMA.

**Table 1: Spinal Muscular Atrophy Classification**

| **Type** | **Age at Symptom Onset** | | **Maximum Motor Function** | **Life Expectancy** | ***SMN2* Copy No.** |
|---|---|---|---|---|---|
| 0 | Fetal | | Nil | Days – Weeks | 1 |
| 1 | < 6 Months | 1A: B-2 Weeks<br>1B: < 3 Months<br>1C: > 3 Months | Never sits | < 2 years | 1, **2**, 3 |
| 2 | 6 – 18 Months | | Never walks | 20 – 40 years | 2, **3**, 4 |
| 3 | 1.5 – 10 Years | 3A: < 3 Years<br>3B: > 3 Years | Walks, regression | Normal | 3, **4**, 5 |

| 4 | ➢ 35 Years | Slow decline | Normal | 4, 5 |
|---|---|---|---|---|

Source: Adapted from Kolb 2011
*SMN2* = survival motor neuron 2 gene
**Bold** = the predominant number of *SMN2* copies

SMA Type 1 patients, by definition, never attain independent sitting and have hypotonia within the first 6 months of life. SMA Type 1 is the leading genetic cause of infant death with an onset at ≤ 6 months of age (Table 1). In contrast, SMA Type 2 manifests within the first 18 months, and children afflicted with this condition are able to maintain sitting unassisted but never walk independently. SMA Type 3 patients attain the ability to walk unaided (Type 3a have onset 18 months to 3 years of age; Type 3b have onset > 3 years of age). SMA Type 4 is an adult onset disease. The genetic cause for SMA is well established and is intimately involved with one's prognosis. All forms of SMA are autosomal recessive in inheritance and are caused by deletions or mutations of the *SMN1* gene.

Studies have shown that SMN protein is required for motor neuron function (Lefebvre et al., 1995; Burghes and Beattie, 2009). Lack of full-length functional SMN protein has been attributed to selective loss of motor neurons (Lefebvre et al., 1997) and the loss of motor neurons results in progressive muscle weakness, the inability to develop basic motor functions and consequently death. AVXS-101 was designed to efficiently deliver a fully functional *SMN* gene to motor neurons in the CNS and also target key systemic tissues. Expression of the exogenous gene will increase the level of functional SMN protein in these cells. It is expected that motor neurons, present at time of gene transfer and expressing exogenous SMN protein, will remain viable with normalized developmental potential, arresting or reversing motor neuron cell death and resulting denervation of skeletal muscle.

Safety of AVXS-101 was assessed in SMA Type 1 patients via intravenous infusion in the Phase 1 clinical study. AVXS-101 appears to have a favorable safety profile and to be generally well-tolerated; treated patients have demonstrated improvement in motor function and achievement of developmental milestones. Additionally, patients treated to-date with AVXS-101 have demonstrated improved nutritional status including lower instances of required feeding support (e.g., G-tube, NJ tube) due to the inability to swallow when compared with untreated patients (Mendell 2017). Thus, AveXis will continue development of AVXS-101 to improve disease course, prolong survival, and delay the need for respiratory assistance in SMA patients.

## 4. Information on potential risk of AVXS-101 in humans

As the vector construct is replication defective, even in the presence of a helper virus, no new progeny viruses are being produced, Thus, the pathogenicity of AVXS-101 is expected to be even less than that of AAV2 or AAV9 viruses, which are already considered non-pathogenic.

### 4.1 Information on potential integration of AVXS-101 into the genome

Preclinical data indicate that in most cases, DNA delivered by recombinant AAV vectors predominantly persists as extrachromosomal elements (episomes) rather than integrating into host cell genomes (McCarty, et al., 2004). Although AVXS-101 is also not anticipated to integrate into

the host cell genome as described above, the long-term consequences of administering AAV viral vectors to humans are not yet fully understood. This is in contrast to wild-type AAV, also non-pathogenic, which has the ability to stably integrate into the host cell genome at a specific site (designated AAVS1) in the human chromosome 19 (Kotin, et al., 1990; Surosky, et al., 1997).

Since the AVXS-101 product uses AAV2/9 with all of the wild-type DNA removed from the capsids, except for the Inverted Terminal Repeats, the potential risk of incorporation of AVXS-101 into the patient chromosomal DNA is thought to be significantly reduced.

There are conflicting reports that integration of the wild-type AAV2 genome is associated with induction of hepatocellular carcinoma in a small subset of patients.; however there are several studies with evidence to contradict these claims including; a) AAV2 has infected approximately 90% of the human population, b) AAV2 has been shown to possess anticancer activity, c) epidemiological evidence suggests that AAV2 infection plays a protective role against cervical carcinoma, and d) AAV serotypes including recombinant AAV2 and AAV9 have been or are currently used in 162 clinical trials to date in which no cancer of any type has been observed or reported. For a review of the topic, see Srivastava and Carter, 2017.

Further support for the extremely low potential incorporation into host chromosomal DNA comes from pre-clinical studies, which to date have not shown the development of cancer in treated animals including mice and non-human primates exposed to AVXS-101.

### 4.2 Information on replication of AVXS-101

It is possible the AAV9 vector containing the SMN gene could interact with other viruses with which the patients come in contact, such as rhinoviruses, adenovirus, or herpes. If this happens, the AAV9 vector could form a virus that causes infection if the patient and cells for rescue, replication, and packaging are also exposed to wild-type AAV2. 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. This unlikely scenario has been studied. In cell culture, the rAAV genome can be rescued and replicated by superinfection with wtAAV and a helper virus. However, in vivo rescue experiments have failed to show rescue and replication (Favre et al., 2001), except in one case in which very large doses of wtAAV and adenovirus were administered in a particular setting (Afione et al., 1996). Therefore, AAV9 interaction with other viruses to cause infection appears to be a minimal risk for AVXS-101.

### 4.3 Information on expected effect from exposure to AVXS-101

*In treated persons:* AVXS-101 is expected to target the motor neurons in the CNS and also target key systemic tissues. Following treatment, the vector is expected to persist for months or years, primarily as stable episomal structures in the cells that are transcriptionally active

The presence of the hSMN gene under the transcriptional control under the control of the cytomegalovirus (CMV) enhancer/chicken-β-actin-hybrid promoter (CB) is expected to result in expression of functional hSMN. Increased levels of functional SMN protein in the target cells are expected to arrest or reverse motor neuron cell death and denervation of skeletal muscle.

Human SMN protein is not known to have toxic effects.

Based on data from the Phase 1 study AVXS-101-CL-101 currently available through 07 Aug 2017, 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.

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.

*In non targeted persons:* Although human infections are common, AAV is not known to be a pathogenic virus in humans and has never been implicated as an etiological agent for any disease. Almost no human innate immune response is seen in AAV infection and at the adaptive level it is primarily made up of a humoral response. Pre-existing antibodies in patients, because of prior infection, account for the humoral response seen toward AAV. Cell-mediated responses to AAV vectors have been documented, but this response may be dependent on the route of administration. Despite the lack of evidence for pathogenicity, correlations have been made between:

(i) presence of AAV viral DNA sequences in testicular tissue and abnormal semen samples,

*(ii)* the occurrence infectious AAV in embryonic material as well as in the cervical epithelium.

A clear association is hard to establish from these studies, given that co-incident evidence of human papillomavirus infection is present in most subjects, and that AAV DNA can be detected in cervical samples in the majority of women but is very dependent on differences in sample collection between studies. An additional, theoretical, risk of AAV infection is the risk of insertional mutagenesis caused by non-site specific integration of the AAV genome into the host-cell genome of infected cells. Preclinical data indicate that in most cases, DNA delivered by recombinant AAV vectors predominantly persists as extrachromosomal elements (episomes) rather than integrating into host cell genomes.

There are conflicting reports that integration of the wild-type AAV2 genome is associated with induction of hepatocellular carcinoma in a small subset of patients. However, there are several studies with evidence to contradict these claims including:

(i) AAV2 has infected approximately 90% of the human population,

(ii) AAV2 has been shown to possess anticancer activity,

(iii) epidemiological evidence suggests that AAV2 infection plays a protective role against cervical carcinoma,

(iv) AAV serotypes including recombinant AAV2 and AAV9 have been or are currently used in 162 clinical trials to date in which no cancer of any type has been observed or reported.

It is possible the AAV9 vector containing the *SMN* gene could interact with other viruses with which the patients come in contact, such as rhinoviruses, adenovirus, or herpes. If this happens, the AAV9 vector could form a virus that causes infection if the patient and cells for rescue, replication, and packaging are also exposed to wild-type AAV2. 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. This unlikely scenario has been studied. In cell culture, the rAAV genome can be rescued and replicated by superinfection with wtAAV and a helper virus. However, in vivo rescue experiments have failed to show rescue and replication, except in one case in which very large doses of wtAAV and adenovirus were administered in a particular setting. Therefore, AAV9 interaction with other viruses to cause infection appears to be a minimal risk for AVXS-101.

As wild type AAV, AVXS-101 is not known to be pathogenic to humans. AVXS-101 is a recombinant biological product intended for gene replacement therapy in infants. It 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. 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).

AVXS-101 does not contain any of the viral genes necessary for replication 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.

Since the AVXS-101 product uses AAV9 with all of the wild-type DNA removed from the capsids, except for the Inverted Terminal Repeats, the potential risk of incorporation of AVXS-101 into the patient chromosomal DNA is thought to be significantly reduced. Further support for the extremely low potential incorporation into host chromosomal DNA comes from pre-clinical studies, which to date have not shown the development of cancer in treated animals including mice and non-human primates exposed to AVXS-101.

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 infectious AVXS-101 shedding from subjects.

A limited number of persons are expected to be in contact with AVXS-101. Medical personnel allowed to manipulate IMP will be trained accordingly. Patient´s family and care giver(s) will be instructed to use protective gloves if/when they come into direct contact with the patient´s body fluids and/or waste, as well as good hand-hygiene for a minimum of four weeks after gene

replacement therapy. Additionally, patients are prohibited from donating blood for two years following vector infusion.

# 5. Information on potential risk of AVXS-101 to the environment

## 5.1 Information on shedding of AVXS-101

Previous experimental data evaluating the shedding of recombinant AAV viral vectors in animals (both rodent and non-human primate) receiving systemic (IV) injections of high titer rAAV vector, demonstrated only transient and low levels of rAAV shed in bodily fluids including urine, semen, blood and feces (Tenenbaum et al. 2003; Reuter et al. 2012).

In addition, as part of a previous and ongoing clinical trial for AVXS-101 (AVXS-101-CL-101), the trial sponsor collected saliva, urine, and stool samples at weekly timepoints through Day 30 and then monthly timepoints through Month 18 after gene transfer during the AVXS-101-CL-101 clinical study from five subjects for viral shedding analysis. This analysis detects the number of vector genome copies by highly sensitive digital droplet (ddPCR) in the applicable biological samples. AVXS-101 DNA is detectable in the shed samples from day 1 post injection. All five subjects analyzed were dosed with 2E14 vg/kg. Concentrations of vector genomes shed in saliva and urine were below the limits of quantitation by ddPCR in these samples within days post dose. While initially concentrated in stool, the amount of vector shed declines logarithmically. Levels of 10.0 – 100.0% of the dosing concentration are detectable up to 14 days post-dose in stool. These concentrations decline approximately 4 logs over 30 days post dose, and all subjects had levels of AVXS-101 DNA in stool below the limit of quantitation by 60 days post dose. Levels representing 0.1−0.01% of the initial dose into the patient are found in urine and saliva at 1 day post dosing, after which levels of AVXS-101 shed into these biological samples are below the limit of quantitation of the assay. Together these data demonstrate rapid decline of shed vector quantities well below dosing concentrations in subjects treated with AVXS 101.

This is in agreement with other studies evaluating AAV viral vector bio-distribution and shedding in non-human primates and in human subjects enrolled in clinical trials utilizing rAAV vectors (Manno et al. 2006; Favre et al. 2001; Salmon et al. 2014), where the levels of shed vector present in bodily fluids rapidly declined to undetectable levels within days or weeks post administration.

Given that the rAAV9 vector used in this study is completely non-replicative and is not a known pathogen of any plant or animal species, and given that the wild type virus is naturally occurring in the environment, the risk to the environment from exposure to potentially contaminated material is considered to be minimal. AVXS-101 vector shedding is observed in fecal material from treated subjects based on data obtained from the AVXS-101-CL-101 study participants, as well as pre-clinical studies and observations from other rAAV clinical trials, where it rapidly declines to levels that can be practically considered as non-infectious, especially given the high multiplicity of infection (MOI) that is necessary for productive transduction. Most importantly, the recombinant AVXS-101 vector is highly attenuated and is incapable of generating a productive infection even in the presence of environmentally occurring helper viruses.

### 5.2 Information of potential dispersal of AVXS-101

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 urine, stool, blood and saliva. 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. Given that the rAAV2/9 vector used in this study is completely non-replicative and is not a known pathogen of any plant or animal species, and given that the wild type virus is naturally occurring in the environment, the risk to the environment from exposure to potentially contaminated material is considered to be minimal. AVXS-101 vector shedding is observed in fecal material from treated subjects based on data obtained from the AVXS-101-CL-101 study participants, as well as pre-clinical studies and observations from other rAAV clinical trials, where it rapidly declines to levels that can be practically considered as non-infectious, especially given the high multiplicity of infection (MOI) that is necessary for productive transduction. Most importantly, the recombinant AVXS-101 vector is highly attenuated and is incapable of generating a productive infection even in the presence of environmentally occurring helper viruses.

SMA is a rare disease and therefore the number of test subjects in this initial study is low in the Belgium [up to 5 patients] and the number expected to be administered therapy if the test results are positive is expected to be 100 patients per year. 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.

It is possible for humans to become infected with scAAV9 if they contact the patient's stool, urine, blood or saliva. In order to minimize this risk, patients are hospitalized for up to 48 hours following gene replacement therapy administration. During the inpatient stay, personnel are required to follow appropriate safety precautions as per institutional standards for infection control; standards should require personal protective equipment (PPE) such as gowns, gloves, masks, glasses, and closed-toe shoes. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved instructions are provided to the patient's family and care giver(s) regarding use of protective gloves if/when they come into direct contact with the patient's bodily fluids and/or waste, as well as good hand-hygiene for a minimum of four weeks after gene replacement therapy.

Only patients with a confirmed diagnosis of SMA as determined by gene mutation analysis with biallelic *SMN1* mutations (deletion or point mutations) are eligible for the study and treatment with AVXS-101 via a onetime IV infusion. This inclusion criteria limits the risk to the environment by limiting the exposure of the GMO to only patients with the disease of interest.

## 6. Information on decontamination of equipment in contact with AVXS-101

After administration of AVXS-101 to the subject, the procedure room will be cleaned according to standard institutional procedures. Since AVXS-101 will be supplied by the manufacturer to the hospital pharmacy in a subject-by-subject manner, no unused product should remain at the hospital center after administration of the patients. Any open vials or unused material must be sealed in leak-proof containers and returned to AveXis/designated depot. In case of accidental spillage of AVXS-101(e.g. on the workbench or on the floor), local procedures will be followed to contain and immediately disinfect the spill to prevent further spread. To decontaminate areas affected (e.g. eradication of the GMOs), spillages in the operation room will be cleaned up with a bleach solution, in accord with European Association of Hospital Pharmacists guidance for handling of gene medicines and the Pharmacy Manual. All contaminated materials will be disposed of locally by incineration or autoclaving. All other places will be cleaned, according to normal decontamination procedures (add reference to decontamination procedures at site).

## 7. Information on constringency plan in case of an unintentional release of AVXS-101

In case of accidental spillage of AVXS-101(e.g. on the workbench or on the floor), local procedures will be followed to contain and immediately disinfect the spill to prevent further spread. To decontaminate areas affected (e.g. eradication of the GMOs), spillages in the operation room will be cleaned up as indicated below:

1. Evacuate area, remove contaminated PPE and allow agents to settle for a minimum of 30 minutes. Initiate spill response procedure.
2. Cover the spill with absorbent material. Starting at the edges and work towards the center.
3. Carefully pour disinfectant (bleach solution followed by alcohol wipes) over the absorbed spill, again starting at the edges. Saturate the area with disinfectant.
4. Allow sufficient contact period to inactivate the material in the spill. Non-viscous spills require 15-20 minutes: viscous spills require 30 minutes.
5. Use paper towels to wipe up the spill, working from the edge to center. Use tongs or forceps to pick up broken plastics, glass or other sharps that could puncture gloves
6. Discard absorbent material in Chemical waste bags.
7. Clean the spill area with fresh paper towels soaked in disinfectant. Thoroughly wet the spill area, allow to disinfect for 15-20 minutes longer, and wipe with towels.
8. Discard all cleanup materials (soaked with disinfectant) in Chemical bag/ container, and any contaminated PPE in a biohazard bag. Close and secure the bags.
9. Place bag in a second biohazard bag, secure and dispose as per institutional guidelines for biohazardous waste.

## 8. Information on additional cautionary steps

Safety measures for biosafety level 1 agents will be utilized. 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.

BSL-1 workers should: Change gloves when contaminated, glove integrity is compromised, or when otherwise necessary. Remove gloves and wash hands when work with hazardous materials has been completed and before leaving the laboratory. Do not wash or reuse disposable gloves. Dispose of used gloves with other contaminated laboratory waste. Hand washing protocols must be rigorously followed.

## 9. Start and end date of the clinical studies

**Clinical study AVXS-101-CL-302**
Start date: H1 2018
End date: Q1 2021

**Clinical study AVXS-101-CL-304**
Start date: H1 2018
End date: Q4 2024