August 23, 2019

Via Electronic Mail
Confidential

Office of Regulatory Affairs
Office of Biological Products Operations (OBPO)
US Food and Drug Administration
orabioninspectionalcorrespondence@fda.hhs.gov

Re: AveXis, Inc.'s Initial Response to the Form FDA 483
Issued on August 2, 2019 to the San Diego, CA Quality Control Laboratory
FEI: 3014617030
Investigators: Scott T. Ballard and Mihaly S. Ligmond

Dear Sir or Madam:

Enclosed please find AveXis, Inc.'s (AveXis or the company) initial response to the Form FDA 483 (483) issued at the conclusion of FDA's July 24 – August 2, 2019 inspection (the July/August 2019 Inspection) of the company's quality control laboratory located in San Diego, California (FEI: 3014617030).

As FDA is aware, the July/August 2019 Inspection followed AveXis's June 28, 2019 self-reporting to the agency of data manipulation issues involving a mouse potency assay—known as the *in vivo* relative potency assay (IVRPA)—used as a product release test during the early clinical phase of Zolgensma® (onasemnogene abeparvovec-xioi).[1] Specifically, it was alleged that two AveXis senior executives altered or instructed others to alter a small amount of raw data used to run the IVRPA. Such conduct is unacceptable, and the two AveXis senior executives have been terminated.

[1] Zolgensma®, Biologics License Application (BLA), STN 125694, is the first gene therapy approved to treat children less than two years of age with spinal muscular atrophy (SMA), the most severe form of SMA and the leading genetic cause of infant mortality.

AveXis would like to make clear that it is committed to transparency with FDA, and to ensuring that data it generates is attributable, legible, contemporaneous, original and accurate. Please note that the investigation into the data manipulation allegations was conducted with focus and diligence. Details regarding the various steps of the investigation into the data manipulation issues are provided in **Section I (pp. 1-9)** of the enclosed response. Please also note that the investigation has not shown an impact on patient safety or product efficacy or quality. Indeed, FDA has stated that the data manipulation issues self-reported by AveXis do "not change the agency's positive assessment of the information from the human clinical trials that were conducted as part of the development program. The totality of the evidence demonstrating the product's effectiveness and its safety profile continues to provide compelling evidence supporting an overall favorable benefit-risk profile."[2]

The company recognizes that the agency has raised concerns regarding the timing of AveXis's June 28, 2019 self-disclosure. AveXis notes that there were 39 working days from the first interview with the reporter to the conclusion of the investigation's first phase determining the veracity of the allegations. There were 36 working days from the start of the quality investigation to the submission of the June 28, 2019 self-disclosure. As more fully detailed in **Section I (pp. 1-9)** of the enclosed response, this was a complex investigation into data integrity allegations, and took significant resources and time. That being said, AveXis understands FDA's concerns and fully appreciates that the circumstances presented by a new gene therapy is something that should be taken into account with regard to the timing of notifying FDA. Although AveXis is confident that the actions detailed in this response will prevent such data manipulation issues from occurring in the future, the company will going forward notify the agency within 5 business days of receipt by our quality organization of any credible allegation related to data integrity impacting a submitted Biologics License Application (BLA).

AveXis takes the feedback contained in the 483 seriously and is committed to comprehensively addressing the noted observations. The company's goal moving forward is to ensure a robust culture of quality and sustainable GxP compliance across AveXis. In light of the data integrity issues mentioned above, and the 483, AveXis, with significant input and oversight from the Novartis Group of companies (Novartis), has developed—and is in the process of implementing—a company-wide Compliance Action Plan (the CAP). As detailed in **Section II (pp. 10-20)** of the enclosed response, the core elements of the CAP are (A) the Quality Integration Plan and (B) the Data Integrity Remediation Plan.

The specific responses to the 483 observations are provided in **Section III (pp. 21-56)** of the enclosed response. For ease of reference, the responses are formatted as follows: each response

[2] Statement on data accuracy issues with recently approved gene therapy (Aug. 6, 2019), https://www.fda.gov/news-events/press-announcements/statement-data-accuracy-issues-recently-approved-gene-therapy.

begins with a restatement of FDA's observation in *italic* text. This is followed by the site's response to the observation(s). At the conclusion of each observation response, planned corrective and preventive actions are detailed with preliminary target completion dates, as appropriate.

AveXis is confident the CAP, together with the actions discussed in the company's specific 483 responses, will be successful and ensure sustainable GxP compliance. To ensure AveXis and FDA are in alignment on the approaches detailed in this response, AveXis respectfully requests a meeting with FDA to update the agency on the investigation into the data manipulation issues, the company's CAP, and the specific actions addressing the 483 observations.

Please do not hesitate to contact me if you have any questions or need further information. I can be contacted by phone at (b) (6) or by email at (b) (6) AveXis will provide periodic updates to FDA on the status of its ongoing actions and investigations, and will also keep FDA apprised of any new actions undertaken. AveXis's first update will be provided to FDA at the end of September 2019.

This document and attachments contain confidential commercial and trade secret information that is protected from public disclosure under the Federal Food, Drug, and Cosmetic Act, the Freedom of Information Act, FDA's implementing regulations, and the Trade Secrets Act. In accordance with FDA's implementing regulations, if a request for disclosure is received, the company asks that it be notified and provided an opportunity to address why the information or materials should not be released.

Sincerely,

Mark Roache Digitally signed by Mark Roache Date: 2019.08.23 15:49:09 -04'00'

Mark P. Roache
Senior Vice President, Chief Quality Officer
AveXis, Inc.

Dave Lennon Digitally signed by Dave Lennon Date: 2019.08.23 14:54:30 -05'00'

David Lennon
President
AveXis, Inc.

I. AveXis's Investigation Into Data Manipulation Allegations

A. AveXis and Zolgensma®

By way of background, AveXis is a biotechnology company focused on developing novel treatments for patients suffering from rare and life-threatening genetic diseases. On May 15, 2018, AveXis was acquired by Novartis.[3] At the time of the acquisition, AveXis's lead gene therapy candidate, AVXS-101, had demonstrated highly compelling clinical data in the treatment of spinal muscular atrophy (SMA). SMA is a rare genetic disease caused by a mutation in the survival motor neuron 1 (SMN1) gene. The gene encodes the survival motor neuron (SMN) protein—a protein found throughout the body, which is critical for the maintenance and function of specialized nerve cells, called motor neurons. Motor neurons in the brain and spinal cord control muscle movement throughout the body. If there is not enough functional SMN protein, then the motor neurons die, leading to debilitating and often fatal muscle weakness. SMA caused by mutations in the SMN1 gene is generally classified into several subtypes, based on the age of onset and severity; infantile-onset SMA Type 1 is the most severe and most common subtype. Children with this condition have problems holding their head up, swallowing and breathing. These symptoms may be present at birth or may present by the age of 6 months. SMA is the leading genetic cause of infant death. If left untreated, SMA Type 1 leads to death or the need for permanent ventilation by the age of two in more than 90% of cases.

On October 1, 2018, AveXis submitted its Biologics License Application (BLA), STN 125694, for Zolgensma® (onasemnogene abeparvovec-xioi) for the treatment of pediatric patients less than 2 years of age with SMA with bi-allelic mutations in the SMN1 gene.[4] The Zolgensma® BLA was approved on May 24, 2019. This was AveXis's first FDA approval.

B. The *In Vivo* Relative Potency Assay

Between approximately March 2017 and June 2018, AveXis used a mouse potency assay—known as the *in vivo* relative potency assay (IVRPA)—for release and stability testing of clinical product. The IVRPA used SMNΔ7 mice to determine the relative potency of lots of AVXS-101 for release and stability testing. SMNΔ7 mice have a genetic mutation that models SMA disease, resulting in a greatly reduced life expectancy compared to mice without the mutation. Untreated, SMNΔ7 mice will die of SMA-like disease approximately 15 days after birth. As part of the IVRPA, the date that each mouse died was recorded, and these dates of death were used to assess the median number of days of survival for each of the groups of mice. The information for each mouse used in the IVRPA was first manually recorded on "cage cards" affixed to each mouse

[3] Novartis successfully completes acquisition of AveXis, Inc. (May 15, 2018), https://www.novartis.com/news/media-releases/novartis-successfully-completes-acquisition-avexis-inc.

[4] *See* BLA 125694, Summary Basis for Regulatory Action at 4.

cage, and then transcribed onto an individual raw data sheet for each mouse. The data from the individual mouse sheets were used to calculate the median dates of survival, and the response was expressed as a relative potency percentage, with reference to a pre-selected reference standard lot of AVXS-101.

Although adequate for its intended purpose of supporting AVXS-101 development, the IVRPA was known to have a large degree of variability. At FDA's request, AveXis developed and validated an *in vitro* relative potency assay that, together with a confirmatory *in vivo* functionality assay, replaced the IVRPA for product release and stability testing. IVRPA has not been used for clinical product release purposes since June 2018, nearly a year before Zolgensma® was approved, and was never used for the release of commercial product. The IVRPA was a small part of the overall testing of AVXS-101.

Both the *in vitro* cell-based assay and the new *in vivo* functionality assay were validated and included in the Zolgensma® BLA as the tests to be used to assess potency for both release and stability purposes. Together, the assays are considered to be a significant improvement over the IVRPA, including by reducing testing variability. The IVRPA was not included in the BLA as a commercial final product release test or as a currently-used stability test.

AveXis takes the integrity of all clinical and GxP data extremely seriously. The allegations made in March 2019 concerned a small portion of the clinical product testing data, and as already mentioned involved a test that has not been used for clinical product release purposes since June 2018 and is not identified in the BLA as a commercial final product release test or as a currently-used stability test. Further, none of the data discrepancies identified during the investigation was determined to impact original lot release determinations. Notably, re-assessment of the underlying data did not change any reported within-specification result (passing result) to an out-of-specification result (failing result). Subsequent testing of all impacted clinical development lots using the validated *in vitro* relative potency assay have also consistently demonstrated that each lot meets the specification for relative potency.

Indeed, as described in detail, below, throughout the course of investigating the alleged data manipulation, there has been a consistent determination that the allegations had no impact on patient safety or product efficacy or quality.

C. Receipt of the Data Manipulation Allegations

As FDA is aware, on March 14, 2019, roughly 8 months after the discontinuation of the IVRPA, AveXis senior management first learned of alleged data manipulation issues involving certain mice used in the IVRPA. Specifically, an AveXis employee alleged that two AveXis senior executives altered or instructed others to alter certain raw data derived from the IVRPA. The

allegation primarily concerned the recorded date of death for some of the mice used in the IVRPA. Notably, there was no allegation that data manipulation had or could have any impact on the safety or effectiveness of the product.

Consistent with FDA-recognized standard industry practice, AveXis opened and scoped the internal investigation to be conducted in a manner reasonable in the circumstances presented. For the first phase, AveXis engaged external counsel to lead an independent investigation. This was believed to be necessary because the two executives who were the subject of the allegations were still fixtures at AveXis with the potential to influence and impede the investigation. Given that the allegations involved data manipulation, the companies wanted to ensure that key evidence was preserved and made available for a thorough technical review. Toward that end, the two executives who were the subject of the allegations were not informed of the investigation during this initial phase. And because both had access to and would in the normal course be alerted to the opening of a formal quality investigation, AveXis chose not to open a formal non-conformance investigation through its quality system at that time.

D. The Initial Investigation Phase

Immediately upon learning of what was then an *allegation* of data manipulation, AveXis launched an internal investigation on March 14, 2019, led by senior officials from AveXis HR, Quality, and Legal, to fully understand the allegations and determine their merit, and to assess the veracity of the claims and potential scope of the data manipulation. AveXis personnel immediately contacted the individual who made the allegations, but were informed that the individual was unavailable until March 26, 2019. AveXis personnel pursued other initial investigational steps, including the development of an investigation plan, gathering necessary materials, preparing the necessary *Upjohn* warnings, and additional investigational activities. The individual who reported the allegations was interviewed on March 26, 2019. After conducting the interview and completing a thorough review of the testing records described by the reporter, AveXis determined that the allegations merited further investigation and informed Novartis on March 28, 2019.

For this phase of the investigation, an external law firm was then engaged to conduct an internal investigation into the allegations, on April 3, 2019. Because the allegations involved two founders who were still senior executives and fixtures at AveXis, and because the allegations involved data manipulation, this initial internal investigation was led by external counsel to ensure that key evidence was preserved, efficiently gathered, and made available for a thorough technical review without interference from the two implicated senior AveXis executives.

Moreover, the investigation was significantly drawn out due to the implicated senior executives' lack of cooperation and categorical denial of the allegations, which continues to this day. Significant resources were therefore required to review thousands of hand-written and electronic

records concerning the life history of individual mice and comparison of those records to entries on hundreds of spreadsheets. To accomplish this, we estimate that more than 2,000 hours were spent collectively by the investigation team from the engagement of the external counsel until the start of the non-conformance investigation phase discussed below. When discrepancies were identified, technical experts were required to assess the discrepancies to determine whether they had any impact on the results of the underlying IVRPA studies, batch release decisions, and clinical data that may have been generated through use of those batches. In each case, these technical reviews found that the data manipulation issues had no impact on patient safety or product efficacy or quality.

This phase of the investigation consisted primarily of four components and was intended to gather the facts and determine if the allegations could be corroborated or disproved. The four components included:

- Interviews of key AveXis employees;

- Analysis of the underlying data to determine if there were unexplained discrepancies in the data referenced in the allegations (between data recorded on the mouse "cage" card and the individual mouse data sheets used in the IVRPA);

- Review of tens of thousands of documents and electronic records from relevant AveXis employees; and

- An impact assessment conducted by technical experts to determine the impact of any discrepancies identified on the results of the underlying IVRPA studies, batch release decisions, or clinical data that may have been generated through use of those batches, as well as the impact of any data discrepancies on patient safety, product efficacy, or quality.

Thus, the initial phase of the internal investigation focused on confirming the allegations, and involved a number of time-intensive steps and significant resources, including:

- Preparing an investigation plan;

- Reviewing inspectional logs and observations from FDA inspections, non-conformance reports (NCRs), and regulatory documents from the BLA file in order to understand the allegations and their potential implications;

- Reviewing background materials to fully understand the potency assays and how they were conducted;

- Reviewing relevant policies and procedures, including with regard to documentation of data and the conduct of the potency assays, in order to understand potential discrepancies in the data;

- Preparing for and conducting interviews with key individuals;

- Identifying and obtaining the relevant data and documents for analysis; and

- Data analysis and preparation of spreadsheets comparing the sources of the potency assay data.

Again, at every point of the initial internal investigation, the assessment of the technical experts was that there was no impact on patient safety or product efficacy or quality. Moreover, during this time, AveXis was actively engaged in the investigation and in monitoring the results of the investigation. The initial investigation and interviews demonstrated that the two senior AveXis executives alleged to have been responsible could not offer a credible explanation for revisions to and inconsistencies in the data, and they were placed on administrative leave on May 3, 2019 to ensure that they had no access to data, systems, or staff. These two senior AveXis executives were later terminated for cause on August 13, 2019.[5] As a reminder, this phase of the investigation took 39 working days.

E. The Non-Conformance Investigation Phase

Following the initial investigation's determination that the allegations were credible and merited continued investigation, as a second phase, a non-conformance (NC) investigation was initiated on May 8, 2019 to further investigate the issues, including conducting a comprehensive root-cause analysis, conducting a more detailed risk assessment, and developing and implementing corrective and preventive actions to address the data integrity issues. A non-conformance report—NCR-1922—was opened in AveXis's ACE document management system on May 15, 2019 to document the investigation activities. A team consisting of AveXis senior Quality leadership, AveXis San Diego Quality Assurance and Quality Control, and Novartis GxP Compliance conducted the NC investigation.

The NC investigation—which remains open—is focused on concerns relating to *in vivo* mouse studies 1-10, which implicated IVRPA data for four product lots: Lot NCHAAV95MN0613 stability data at the 3-month time point; Lot 600307 release data; Lot 600729 release data; and Lot 600539 release data. Three of these lots had been consumed or were expired, with all

[5] As noted in the public statements of his counsel, one of these executives continues to deny any wrongdoing.

material in the remaining lot placed on hold at the AveXis Libertyville, Illinois site as of May 5, 2019.

AveXis continued to follow standard industry practice, operating procedures, and precedent, all of which supported completion of the preliminary NC investigation before submission of a report to the FDA given that there was no evidence of impact on patient safety, product efficacy or quality.

The NC investigation proceeded according to the following methodology:

- Review of all possible sources of data pertaining to the assay in question, such as GMP data sheets for the IVRPA, original records used in the management of animals (cage cards), spreadsheets created by employees to hold data and calculate results of the assays, and laboratory logbooks;

- Identification of possible data discrepancies;

- Determination of possible alternative values for reported relative potency for lots involved in studies implicated;

- Evaluation of clinical studies potentially impacted by data integrity allegations;

- Evaluation of regulatory impact;

- Interviews with staff and management; and

- Recalculation of the results and material impact assessments.

Comparative reviews of data sources and interviews have confirmed that there were multiple instances of discrepancies of data used for *in vivo* studies 1-10. In order to either verify existing values, or to determine data values with an increased level of reliability for studies 1-10, a protocol was developed to verify the raw data and to establish procedures for evaluating such discrepancies. Employing this new protocol, raw data were revised when primary records supported revision, potency was recalculated for the IVRPA studies 1-10, and the resulting values from these studies would be annotated as having reduced validity, and that these results should be reported to the appropriate regulatory agencies, which was subsequently done in a timely manner.

NCR-1922's impact assessment further found that despite the IVRPA data concerns, the original clinical conclusions were not in question given the overall technical assessment of all QC release

testing, including the *in vitro* potency assay, and the consistent performance of AVXS-101 in the clinical trials. Specifically, during the development of the product and prior to submission of the BLA, FDA previously raised concern regarding the variability of the *in vivo* data from studies 1-10 and requested clinical results from ongoing studies. FDA also requested *in vitro* relative potency data to support the clinical profile of Zolgensma®. Accordingly, while studies 1-10 were used in the development of the product, these data would not have been relied upon to reach any clinical determinations given this variability.

Finally, because the NC investigation was focused on the immediate allegation and identified data integrity issues, AveXis engaged independent third-party cGMP consultants, including (b) (4) and (b) (4) as described in Section II, below, to expand AveXis's data integrity investigation.

F. AveXis Notifies FDA

The timing of AveXis's self-disclosure to FDA was based in part on the fact that the investigation into the data integrity manipulation issues was highly complex, and involved review of a significant amount of data, including manual comparisons of raw data on the individual mouse data sheets and cage cards, and identification of technical experts to assess the impact. In addition to the sheer volume of data to be reviewed, the investigation required distinguishing between discrepancies that were attributable to a lack of clear instructions in the relevant procedures and those that were the result of deliberate wrongdoing. For example, discrepancies in another investigation were ultimately attributed to a lack of clarity as to whether to include the day of birth in the survival days calculation. In addition, just as with the initial phase of the, throughout the NC investigation, the assessment of technical experts was that there was no impact on patient safety or product efficacy or quality. Accordingly, AveXis self-reported the matter to FDA once the interim NCR was issued. The interim investigation report—interim NCR-1922—was issued on June 27, 2019. The next day, June 28, 2019, AveXis self-reported to FDA the allegations and the interim results of its investigation via submission through the electronic gateway. The lead clinical reviewer was informed by phone just prior to electronic submission. The interim results of the investigation were also provided to the regulatory authorities in all jurisdictions where applications for marketing of Zolgensma® had been made, including two jurisdictions where the application is still pending.

G. Additional b) (4)

As part of the investigation, (b) (4)

(b) (4)

To further investigate (b) (4)

investigation was ongoing. As previously communicated to FDA, based on information obtained pursuant to the investigation, AveXis concluded that it was likely that (b) (4)

Although AveXis's investigation was ongoing during the July/August inspection, AveXis provided a draft copy of NCR-2018 to the FDA investigators, who requested and retained a copy of the draft investigation report and related documentation. AveXis will (b) (4)

H. FDA Inspects AveXis

Subsequent to AveXis's self-reporting of the data integrity issues and the interim results of its investigation to FDA, FDA conducted an inspection of AveXis's San Diego site from July 24 to August 2, 2019 based on the company's June 28, 2019, submission. This inspection resulted in the issuance of a five-item Form FDA 483, which is addressed in Section III, below.

I. FDA Makes Statement Regarding the Data Issues—Patient Safety and Product Efficacy not Implicated

On August 6, 2019, the Director of FDA's Center for Biologics Evaluation and Research (CBER) issued a public statement about the data accuracy issues relating to the product testing

during the development of Zolgensma®, recognizing that its concerns at the time were "limited to only a small portion of the product testing data that was contained in the marketing application."[6] FDA stated that at this stage the data manipulation issues self-reported by AveXis do "not change the agency's positive assessment of the information from the human clinical trials that were conducted as part of the development program. The totality of the evidence demonstrating the product's effectiveness and its safety profile continues to provide compelling evidence supporting an overall favorable benefit-risk profile." FDA expressed that it "remains confident that Zolgensma should remain on the market."[7]

[6] Statement on data accuracy issues with recently approved gene therapy (Aug. 6, 2019), https://www.fda.gov/news-events/press-announcements/statement-data-accuracy-issues-recently-approved-gene-therapy.

[7] *Id.*

II. The Compliance Action Plan

AveXis's goal is to ensure that a robust culture of quality and sustainable GxP compliance exist at all of its sites. Accordingly, in light of the data integrity issues discussed in Section I, above, and the 483, AveXis, with significant input and oversight from Novartis, has developed—and is in the process of implementing—a company-wide Compliance Action Plan (the CAP).[8] As detailed below, the core elements of the CAP are (A) the Quality Integration Plan and (B) the Data Integrity Remediation Plan. AveXis is confident the CAP, together with the actions discussed in AveXis's specific responses to the 483 observations, will fully address any data integrity and broader GxP compliance concerns raised in the 483.

A. The Quality Integration Plan

AveXis recognizes that the 483 highlights areas for improvement in the company's quality systems and quality culture. Accordingly, the CAP seeks to make enhancements in these areas, and one key aspect of strengthening AveXis's quality systems and quality culture is by further integrating the AveXis sites into Novartis's global quality network. The plan for doing so is set forth below.

As FDA is aware and as stated above, AveXis was acquired by Novartis in May 2018. In early 2019, Novartis began the process of more closely aligning the AveXis quality organization with the Novartis global quality network. Until recently, Novartis's alignment with AveXis focused primarily on establishing and defining the lines of communication between the AveXis and Novartis quality organizations from a functional perspective.

In light of the data integrity issues discussed in Section I, above, and the 483, Novartis senior leadership has made the decision to completely integrate AveXis into Novartis's global quality network and will accelerate several key integration actions to ensure that this integration occurs quickly and effectively. Novartis understands the need to further instill a culture of quality in AveXis's operations, and that creating and sustaining such a culture is a complex task requiring a structured plan, engagement of personnel at every level, and visible leadership support. In this regard, the Quality Integration Plan is attached at Exhibit 1.

These actions include integrating the AveXis quality organization into the Novartis global quality organization from an operational perspective. As a result of this restructuring of the relationship between the AveXis and Novartis quality organizations, the AveXis quality organization will formally become a part of the Novartis quality organization. As such, the

[8] The enhancements detailed in the CAP, including the Quality Integration Plan, will also be implemented at AveXis's two under-construction sites in Durham, NC and Longmont, CO as those sites come online.

AveXis Data Integrity Officer, for example, will be a part of the Novartis data integrity community. Similarly, Novartis's global quality management systems (QMS) will be implemented at AveXis to ensure that the AveXis quality organization is using the same QMS.

In conjunction with this integration, Novartis will perform an organizational assessment of the AveXis quality organization with the goal of completely aligning the structure of the AveXis quality organization with the structure of Novartis's quality organization. Please note that this organizational structure assessment is separate from the organizational capabilities assessment discussed in the response to Observation 1, which will be performed by (b) (4) and will assess the effectiveness and capabilities of the AveXis quality organization from a resources and staffing perspective.

AveXis has also hired senior executive compliance personnel with previous Novartis experience to facilitate the further integration of AveXis into the Novartis organization. Additionally, the AveXis Head of QA Compliance will sit on the Novartis QA Compliance extended leadership team.

At a procedural level, Novartis will conduct gap assessments of AveXis's key quality policies and procedures against Novartis's corresponding global quality policies and procedures to ensure alignment. Following this gap assessment, Novartis will oversee the revision and implementation of any AveXis policies or procedures, as needed. Novartis has already identified several procedures for revision, including POL-007, *Data Integrity Policy*, SOP-087, *QC Laboratory Documentation*, SOP-003, *Good Documentation Practices*, SOP-365, *Notification to Management*, and SOP-005, *Non-Conformance and CAPA System*. A number of Novartis procedures, constituting Novartis's Core Quality & Compliance Systems, have been identified for expansion to AveXis. These include procedures relating to the process for management escalation, data and documentation, and pharmacovigilance.

Novartis will also conduct baseline audits at the AveXis sites to assist with the determination of which integration activities should be prioritized based on the audit results and Novartis's risk classification of the audit results. *See* Exhibit 2.

In addition to these in-process organizational, procedural, and operational changes, Novartis is in the process of establishing and rolling out the Novartis "SpeakUp" program across AveXis. Novartis SpeakUp will provide AveXis employees a clearly defined pathway for reporting concerns regarding potential misconduct or fraud. Reports received through the Novartis SpeakUp portal are evaluated by Novartis's SpeakUp Office, an independent office within Novartis. All AveXis employees will be trained on how to report suspected misconduct, fraud, and other concerns through the Novartis SpeakUp portal, and on the importance of immediately reporting suspected misconduct or fraud through the Novartis SpeakUp portal. Once fully

deployed, Novartis SpeakUp will help improve transparency, provide an independent misconduct reporting pathway for AveXis employees, and ensure that Novartis has full visibility into any reports of misconduct or fraud at AveXis.

In addition, AveXis has approved Novartis quality incident SOP 7038922, *Quality/GxP Escalation and Incident Management*, to ensure that, going forward, potential quality issues, including any issues relating to or potentially relating to the integrity of quality data generated at AveXis's sites, are timely escalated to senior quality leadership. Implementation of this procedure is underway.

Novartis is confident that the integration actions detailed above will result in significant, sustainable improvement across AveXis's quality systems. As noted in the Cover Letter, AveXis will provide periodic updates to FDA on the status of its ongoing activities and will also keep FDA apprised of any new actions related to integration that are developed and implemented.

B. The Data Integrity Remediation Plan

AveXis fully recognizes the importance of ensuring the accuracy, reliability, and traceability of quality data, including all data submitted to FDA as well as all data generated pursuant to commercial manufacturing activities. Accordingly, as part of the CAP, AveXis, with support from the Novartis global quality organization, has developed and is implementing a Data Integrity Remediation Plan to ensure that the data integrity issues discussed in Section I, above, and the issues identified in the 483 are fully investigated and addressed. The Data Integrity Remediation Plan will be implemented over the coming weeks and months with the goal of assuring FDA that AveXis has broadly addressed FDA's data integrity concerns, and AveXis will update the agency as progress is made and on relevant findings. The Data Integrity Remediation Plan is part of overarching PLAN-313 Version 4.0, *AveXis Data Integrity Plan*, *see* Exhibit 3, which contains additional actions to improve data integrity standards throughout AveXis.

Based on AveXis's investigations to date, the data integrity issues discussed in Section I, above, and the examples noted in the 483 appear to be limited to a few discrete incidents where (1) due to a lack of GxP experience, a lack of understanding of the importance of data integrity and good documentation practices, and a lack of robust controls and oversight, documentation anomalies went unnoticed, and (2) two members of AveXis's executive leadership team—both of whom have been terminated—either manipulated or pressured laboratory personnel to manipulate data. Additional root causes identified to date include a lack of a cultural emphasis on data integrity at the site, a lack of adequate training and real-time data recording, and a lack of a formal escalation policy for GxP issues. Further, as detailed below, AveXis is confident that the data

integrity issues discussed above and noted in the 483 do not impact the safety, efficacy, or quality of Zolgensma®.

AveXis understands the significance of the data integrity issues discussed in Section I, above, and the 483 observations and is taking numerous actions to address them and prevent recurrence. The company would also note that prior to the start of the July/August 2019 inspection, numerous controls had already been implemented across the San Diego site to ensure the accuracy, reliability, and traceability of quality records and data. These include:

- SOP-279, *Computerized System Qualification and Validation*, which sets forth the qualification and validation requirements for computerized systems used for GxP activities. These requirements ensure that GxP computerized systems perform as expected in accordance with predetermined specifications, user-defined requirements, and applicable FDA regulations, including 21 CFR Part 11.

- Plan 313, *Data Integrity Plan and Assessment*, pursuant to which AveXis performed a global data integrity assessment of computerized systems used for GxP operations, including laboratory computerized systems, for adherence to ALCOA data integrity principles and 21 CFR Part 11 compliance.

- SOP-003, *Good Documentation Practices*, which provides that:

    - Falsification of records is strictly prohibited. Pursuant to SOP-003, falsification includes back dating or entering a future date; signing someone else's name; signing a document or record before the activity is performed; signing for, witnessing, or verifying a step without witnessing or verifying the activity; copying and/or pasting scanned signatures for use as approval signatures; entering data/information not directly obtained, that did not occur, or that was not observed; entering data when testing was not performed, completed, or that is not reflective of the actual result obtained; and destroying or voiding original data or information without documenting such action.

    - All data/information are to be recorded by the person who has performed the activity/task unless the document clearly indicates that information is being recorded by someone other than the performer AND the performer's signature is also present.

    - All entries must be made at the time tasks are performed. Records must indicate the date and/or time tasks were performed/recorded as indicated by specification, procedure, or record format.

- Raw data must be retained in its entirety and original form, e.g. printouts of all attempts at system suitability (whether passing or not) OR all calibration attempts, including failures.

- SOP-238, *Data Integrity Controls*, which provides that all data generated at AveXis must be accurate, legible, contemporaneous, original, and attributable (ALCOA). SOP-238 also prohibits deleting, manipulating, or modifying GxP data.

In addition, the investigators performed an extensive review of AveXis's raw data, including *in vivo* functionality data for all commercial lots of Zolgensma®, *in vivo* functionality and *in vitro* relative potency data for all lots of Zolgensma® for which Lot Release Protocols have been submitted to FDA, raw data for all lots of AVXS-101 tested using SOP-346 and SOP-347, method validation data for SOP-346, *In-vivo Functionality Test using a Single Dose AVXS-101 in SMNΔ7 Mouse Model*, and SOP-347, *Determination of In-vitro Relative Potency for AVXS-101 Drug Substance and Drug Product*, and the raw data, including audit trails, for testing performed pursuant to (b) (4) .

AveXis also recognizes that the 483 identifies several gaps with respect to the company's data integrity and documentation practices, including comprehensiveness and robustness of the controls noted above. AveXis's Data Integrity Remediation Plan, set forth below, will address these gaps and any additional gaps identified pursuant to AveXis's implementation of the CAP.

The Data Integrity Remediation Plan includes the following elements:

- A comprehensive investigation into the extent of the inaccuracies in data records and reporting, including:

    - A detailed investigation protocol and methodology, including a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment;

    - Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies.

    - An assessment of the extent of data integrity deficiencies at the San Diego site; and

    - A comprehensive retrospective evaluation of the nature of the data integrity deficiencies.

- A risk assessment of the potential effects of the observed data integrity deficiencies on the quality of Zolgensma®, the data submitted to FDA in the Zolgensma® BLA (BLA 125694), and AveXis's other investigational products.

- A management strategy establishing AveXis's global corrective action and preventive action plan, including:

    - A detailed corrective action plan describing AveXis's strategy for ensuring the reliability and completeness of quality data, including data submitted to FDA;

    - Interim measures to protect patients and to ensure the quality of Zolgensma®; and

    - Long-term measures describing any remediation efforts and enhancements to procedures, processes, methods, controls, systems, management oversight, quality culture, and human resources (*e.g.*, training, staffing improvements) designed to ensure data integrity.

As discussed in the sections below, a number of corrective and preventive actions (CAPAs) have already been implemented to address the 483 observations, and the company will be implementing numerous additional CAPAs over the coming weeks and months. The effectiveness of these and any additional CAPAs implemented pursuant to the CAP will be verified by Novartis's global quality department and by third parties. AveXis will provide periodic updates to FDA on the status of the actions undertaken pursuant to the CAP.

Third-Party Investigation

While AveXis remains confident in the thoroughness of the investigation activities and findings discussed in Section I, above, the company engaged (b) (4) an independent third-party cGMP consultant, to perform an assessment of the data manipulation and documentation issues noted in NCR-1922, which has been expanded to cover the issues noted in the 483. (b) (4) assessment of the San Diego site's data integrity controls and oversight was originally scheduled to start on July 29, 2019, but was rescheduled due to the FDA inspection. (b) (4) assessment is now scheduled to begin on September 3, 2019.

In light of the 483, the scope of (b) (4) assessment has been expanded to cover AveXis's data integrity controls and oversight more broadly, including documentation practice controls; controls relating to the issuance of controlled forms and documents; computerized systems controls; processes for reviewing data pursuant to release, including the scope of QA review of electronic and paper records; and AveXis's internal audit function.

In addition to assessing AveXis's data integrity controls and oversight, (b) (4) will investigate whether the scope of the site's data integrity deficiencies is limited to the specific instances noted in the 483 and previously reported to FDA. Pursuant to this investigation, (b) (4) will evaluate raw data, including data submitted to FDA in the Zolgensma® BLA, for evidence of discrepancies or manipulation. At AveXis's request, (b) (4) data integrity investigation will cover manufacturing, laboratory, and clinical data. (b) (4) investigation will be conducted pursuant to the written protocol detailing (b) (4) investigation methodology and summarizing all of the laboratories, manufacturing operations, and systems to be covered by the investigation. As detailed in the investigation protocol, in light of the 483 observations, (b) (4) investigation will include a comparison of raw data and reported data to ensure that any inconsistencies have been identified. (b) (4) findings and recommended actions will be documented in a written report.

Further, although the 483 is limited to the San Diego site, AveXis recognizes that the actions detailed in the CAP and in the response should be implemented across the company. Accordingly, (b) (4) will also be performing similar assessments across the AveXis sites, including with respect to the company's commercial manufacturing, laboratory, and clinical data.

Risk Assessment

As noted above, AveXis provided the interim NCR-1922 investigation report to FDA on June 28, 2019. This document summarized AveXis's assessment of the product quality risk as of June 27, 2019. Briefly, because the primary potency assays during clinical development were the *in vitro* relative potency assay and the *in vivo* functionality assay, and because these tests, not the *in vivo* relative potency assay, are identified in the Zolgensma® BLA as the commercial final product release tests for potency, AveXis determined that the product quality risk was low. This is consistent with FDA's August 6, 2019, press release stating that the "totality of the evidence demonstrating the product's effectiveness and its safety profile continues to provide compelling evidence supporting an overall favorable benefit-risk profile."[9]

Based on (b) (4) review, as detailed above, AveXis will conduct a further risk assessment to ensure that any new or additional findings by (b) (4) are fully evaluated. This risk assessment will also assess whether any additional portions of the Zolgensma® BLA should be amended to ensure that all data before the agency are accurate, complete, and reliable. AveXis will then provide FDA with the findings of the risk assessment.

[9] Statement on data accuracy issues with recently approved gene therapy (Aug. 6, 2019), https://www.fda.gov/news-events/press-announcements/statement-data-accuracy-issues-recently-approved-gene-therapy.

Management Strategy

AveXis senior management recognizes the importance of providing direction, leadership, and resources to ensure that the company has the tools it needs to put in place and sustain best practices with respect to data integrity and good documentation practice. Accordingly, AveXis, together with the Novartis global quality organization, is developing and will implement a management strategy to strengthen quality culture at every level across AveXis and to ensure the accuracy, reliability, and completeness of the company's quality records. This management strategy will include:

- **Procedural enhancements.** AveXis will implement additional procedural controls to ensure that quality records and data generated at its site are accurate, reliable, and complete. These improvements include:

    - Revising AveXis's global data management policy to align with Novartis procedures SOP-7018147, *Document and Records Management in Novartis Pharma*, and SOP-7023659, *Good Documentation Practice in Novartis Pharma*, to ensure that data are appropriately managed across all of AveXis's sites. These revisions will provide a framework for managing and retaining data pertaining to every operational unit, including manufacturing and testing data.

    - Revising SOP-238, *Data Integrity Controls*, to further define the controls relating to maintaining the integrity of data and records generated and maintained by AveXis for GxP purposes.

    - Extending Novartis's global escalation procedure 7038922, *Quality/GxP Escalation and Incident Management*, to AveXis to ensure that, going forward, potential quality issues, including any issues relating to or potentially relating to the integrity of quality data generated at AveXis's sites, are timely escalated to senior quality leadership.

    - Revising AveXis's procedures regarding the issuance of controlled forms and records to align with Novartis procedure SOP-7018147, *Document and Records Management in Novartis Pharma*, to ensure that robust controls relating to the issuance, tracking, and reconciliation of controlled records are established and maintained.

    - Revising AveXis's procedures relating to the installation and qualification of manufacturing and laboratory equipment to ensure that such procedures include robust requirements relating to the verification of predicate rule and 21 CFR Part

11 controls and oversight for each piece of manufacturing and laboratory equipment.

- Revising AveXis's internal audit procedures to include robust data integrity self-inspection requirements.

- **Strengthening quality oversight.** To prevent the recurrence of the deficiencies noted in the 483, AveXis will increase quality oversight over the company's day-to-day operations from a data integrity perspective. In particular, in addition the actions set forth above in the Quality Integration Plan section, AveXis will:

  - Establish a Data Integrity Officer role. This person will be responsible for overseeing the implementation of the data integrity controls and oversight set forth in this response, and for ensuring the accuracy, completeness, and reliability of GxP data generated across AveXis's sites.

  - On an interim basis, engage (b) (4) as an independent third party to monitor quality data and records generated across AveXis.

  - Conduct periodic data management and good documentation practice self-inspections to ensure that GxP data are accurate, reliable, and complete.

- **Increasing senior management engagement and oversight.** Corporate leadership and senior management have been and will continue to be closely involved in the ongoing integration and improvement activities at the site. Leadership and senior management have been active both in ensuring needed resources are available and in ensuring this work remains the highest priority. Resources, both human and financial, have and will continue to be applied to the fullest extent needed to achieve our quality and compliance objectives.

  AveXis will enhance its quality management review process by establishing a monthly Quality Review Board to ensure timely escalation of critical and major quality issues to senior management across both quality organizations. Attendance at these monthly Quality Review Board meetings will be mandatory for the QA, QC, Manufacturing, Engineering, and Validation functional area heads, and, until completion of the CAP, AveXis senior management, including the Chief Quality Officer and President, and the Novartis Head of Quality and Novartis Head of QA Compliance. The CAP will be a standing review item at this meeting until its completion.

- **Quality organization and culture improvements.** AveXis is committed to improving the quality culture across the company to ensure that the 483 observations do not recur. AveXis recognizes that building and sustaining a culture of quality requires visible leadership support and engagement of personnel at all levels. To instill a robust culture of quality throughout the company, AveXis will:

    - Train employees across the company on the SpeakUp program, how to report suspected misconduct or fraud through the SpeakUp portal, and on the importance of timely reporting and suspected misconduct or fraud.

    - Develop a quality culture and communication plan to more effectively engage company personnel, communicate management expectations with regard to good documentation practice and data management across the sites, and define accountability. Part of this effort will be increasing senior management's knowledge of data integrity and their engagement and visibility on the importance of data integrity compliance, including site visits by AveXis senior management. Emphasis during the site visits and during the meetings will be on quality, data integrity, and good documentation practice, with particular focus on accountability at the shop floor and middle management levels within the company.

    - Train managers and supervisors on data governance to ensure qualified personnel are aware of the criticality of the company's data governance system, role of senior management, and system review. AveXis will establish separate training modules focusing on foundational data integrity, advanced data integrity, data integrity for auditors, and data integrity for executives.

    - Initiate organizational assessments in an effort to confirm the effectiveness and capabilities of the current quality organization in ensuring and monitoring quality effectiveness and control. The process will involve assessment of the resources, capabilities, and governance of AveXis's quality unit. AveXis has already engaged (b) (4) to perform these assessments.

    - Emphasize and enhance procedures whereby any employee found to be intentionally violating the company's good documentation practice and/or data integrity policies will be subject to removal from their cGMP role and which may include termination.

- **Enhanced training**. AveXis will enhance training opportunities and requirements for staff at all levels at all sites across AveXis, with a focus on increasing employees'

understanding of the importance of good documentation practice and data management. For example, AveXis will:

- Train all employees across the company on the importance of good documentation practice and data management, including the criticality of reliable data and effective data governance.

- Provide additional training for personnel engaged in GxP activities on data management and quality culture. This additional training will be conducted to ensure that appropriate personnel have received comprehensive training on FDA's requirements and how to prevent and detect threats to the integrity of data.

- Add a good documentation practice, data management, and quality culture component to all sites' annual training programs.

- Develop and provide advanced training for QA personnel on data integrity risk detection and mitigation. This training will include data integrity learning maps, educational modules focusing on data integrity case studies based on real-world situations, and tutorials on data integrity risk identification and reporting.

- **Engagement of third-parties.** As noted above, AveXis has already engaged (b) (4) an independent third-party cGMP consultant, to perform a thorough assessment of AveXis's data integrity controls and oversight, and to investigate the extent of the data integrity deficiencies noted in the 483 and the data manipulation issues previously reported to FDA. Separately, AveXis has also engaged (b) (4) to perform a retrospective assessment of critical and major NCRs, which includes out-of-specification test results, to assess the adequacy of AveXis's investigations and determine whether any investigations should be re-opened under (b) (4) supervision and oversight. (b) (4) will also provide an independent review of GxP activities.

III. AveXis's Specific Responses to the 483 Observations

OBSERVATION 1

There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has been already distributed.

A. Non-conformance Report NCR-1922 (which was open at the time of the current inspection) was opened on 15 May 2019 due to a report that was made to the CQO (Chief Quality Officer) alleging that data derived from the AVXS-101 In-Vivo Relative Potency Assay Studies 1-10 may have been mismanaged or even potentially manipulated. Aside from evaluations of Studies 1-10 and a planned evaluation of toxicological studies under NCR-2018 there is no documentation in this NCR that an audit of all other potentially impacted data, studies, and reports was conducted or is planned to determine if there was evidence of data mismanagement or manipulation or a justification for not conducting or planning such an audit. Additionally, there is no documentation in NCR-1922 as to why the NCR was not opened until 15 May 2019 when the initial allegation is documented as having been reported on 14 March 2019.

B. Non-conformance Report NCR-409 was opened on 31 Jan 2018 and has an "Event Description" of "On 31Jan2018, during a historical data review of the potency results for Drug Product Lot 600156 per SOP-285, Determination of In Vivo Relative Potency for AVXS-101 Drug Product, it was discovered that the associated assay form (FORM-212) was not completed at the time of CoA generation and approval for Lot 600156...." During the inspection, the associated FORM-212 was reviewed and it was observed that the date/time stamps on the 4 page form are discrepant in that 3 of the 4 pages have a "Generated" date /time of "05 Jan 2018 09:44AM" and 1 page (page 2) has a "Generated" date/time of " 04 Jan 2018 09:39AM". There is no documentation in NCR-409 that this discrepancy was noticed or investigated. Additionally, current SOP-381 Version 2.0 entitled "Control of QC Test Forms" does not specifically require verification of consistent date/time stamps on each page of a test form during reconciliation of the form.

C. Non-conformance Report NCR-965 was opened on 23 Aug 2018 and has and "Event Description" of "On 23Aug 2018, during the review of Δ7SMA mouse database, it was discovered that there were discrepancies in the data that was used to calculate relative potency for AVXS-101 Drug Product. Lot 816836 had single mouse survival days recorded that were different from the actual value...." As documented in the investigation most of the discrepancies noted were discrepant by a single day which was attributed to ambiguity in SOP-285 "Determination of ln-Vivo Relative Potency for AVXS-101 Drug Product" however in 4 cases discrepancies of greater than 1 day were noted (ranging from 2-19 days). There is no documentation in NCR-965 that these 4 cases were investigated further to determine a potential root cause.

D. Non-conformance Report NCR-1116 was opened on 15 Oct 2018 and has "Event Description" of " Inconsistencies were identified during the review and approval of the data previously reported within REC-1606 v1.0 'Mouse Survival Data: Results for In-vivo Relative Potency for AVXS-101 Drug Product'...." As documented in the investigation " ... During investigational review of the Quality Employee's process, it was determined that some of the early raw data results were initially communicated verbally from the ... to the AveXis Quality Employee...." There is no documentation in NCR-1116 explaining why the Quality Employee accepted verbal communication of raw data without corresponding written documentation.

General Response to Observation 1

AveXis recognizes the importance of ensuring that quality records are accurate, consistent and reliable, as well as the need to thoroughly investigate any unexplained discrepancies, including data discrepancies. As described in detail in Section II, above, Novartis is accelerating the integration of AveXis into the Novartis quality system through the Quality Integration Plan (QIP). The QIP includes not only a thorough review of AveXis's practices and procedures to ensure alignment with Novartis's quality standards, but also a commitment to enhance the culture of quality and compliance at AveXis through visible, senior management support, comprehensive quality training, and employee accountability.

In particular, the QIP will focus on enhancing site controls for data integrity and good documentation practice, as well as performing thorough quality investigations when unexpected discrepancies occur. AveXis understands that such investigations must extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy; and a written record of the investigation must be made, including the investigation conclusions and follow-up.

Further, through the Data Integrity Remediation Plan, as described in detail in Section II, above, AveXis has engaged (b) (4) to perform an independent, third-party data integrity investigation and assessment at AveXis. The assessment will include a comprehensive review of data and records management practices at AveXis, as well as review of AveXis's historical data integrity investigations. Based on the results of the assessment, AveXis will develop and implement additional CAPAs related to data integrity controls and investigations.

AveXis currently has in place processes to thoroughly investigate non-conformances and ensure CAPAs are implemented. Specifically, SOP-005, *Non-Conformance and CAPA System,* outlines the process for reporting non-conformances. This procedure ensures proper evaluation of product and process impact. This procedure also determines the need for further investigation into root cause and CAPA initiation, as outlined in SOP-005, and ensures that nonconforming

product is appropriately managed and dispositioned. Any incidents relating to the safety, quality, purity or potency of distributed product must be considered for escalation and review by a cross-functional team of management responsible for managing such incidents, in accordance with SOP-365, *Notification to Management*.

The non-conformance investigation process begins by launching a non-conformance or NC in ACE, AveXis's quality tracking system. An initial risk assessment is performed and a determination made whether, in accordance with applicable procedures, a root cause investigation is required. Upon completion of the investigation, if any, appropriate CAPAs are identified for implementation. Product impact assessments and disposition decisions are also contained within the non-conformance. The above-described investigational activities are tracked as tasks within ACE to ensure a thoroughly documented non-conformance investigation has been conducted. In addition, to ensure appropriate quality oversight, progress of quality investigations and CAPAs are monitored at AveXis's monthly Quality Review Board meetings.

AveXis recognizes the opportunity to further strengthen its data management and investigation programs and is committed to providing the necessary human and capital resources to spur continuous improvement at all AveXis sites. For example, through the QIP and Data Integrity Remediation Plan, AveXis will:

- Adopt the practices and requirements from the Novartis Global Operating Procedure, SOP 7039029, *GOP: Deviation Handling*;

- Enhance the established non-conformance management process and the escalation process by aligning AveXis's process with relevant Novartis corporate procedures to ensure that, going forward, potential quality issues, including any issues relating to or potentially relating to the integrity of quality data generated at AveXis's sites, are timely escalated to senior quality leadership;

- Implement a certification process for investigators and QA approvers to ensure that all personnel handling investigation activities undergo focused training on root-cause analysis methodology and the use of investigation tools, including specific training on investigating and remediating data integrity and GDP anomalies, and demonstrate the ability to successfully perform their investigation and oversight responsibilities;

- As an interim control, AveXis has engaged (b) (4) to provide independent oversight to the investigations and quality system, including review and approval of investigations;

- Increase data integrity awareness through senior leadership engagement and company-wide communication efforts;

- Re-train all employees engaged in GxP activities on POL-007, *Data Integrity Policy*, and SOP-003, *Good Documentation Practices*.;

- Establish and train AveXis personnel on the Novartis "SpeakUp" program with an emphasis on the importance of reporting concerns regarding potential misconduct or fraud;

- Create a new Data Integrity Officer position reporting directly to AveXis's Head of QA and responsible for overseeing the implementation of the data integrity controls and oversight set forth in this response, and for ensuring the accuracy, completeness, and reliability of GxP data generated across AveXis's sites; and

- Establish a mentorship program between AveXis quality personnel and Novartis data integrity and investigations subject matter experts (SMEs) to enhance skill building and instill best practices.

AveXis is confident that the above-described controls and enhancements will ensure sustainable compliance with FDA's and the company's own expectations for AveXis's data management and investigation programs. AveXis notes that to assure the effectiveness of the company's data integrity program, focused data integrity modules will be included in routine internal and corporate self-inspections at AveXis sites.

With respect to AveXis's San Diego site, the company wishes to note that until May 2018, the site functioned solely as a research and development facility, with limited quality oversight. Since May 2018, the San Diego site has implemented quality controls consistent with the AveXis quality management system, including for data management and investigations. Furthermore, as described above, key AveXis quality controls will be integrated and aligned with the corresponding Novartis global quality policies and procedures, as part of the overall integration of AveXis with the Novartis quality network.

Observation 1 Corrective and Preventive Actions

In addition to the actions noted above in Section II, including the actions undertaken pursuant to the QIP and the Data Integrity Remediation Plan, AveXis will undertake the following actions to ensure that the issues specifically noted in Observation 1 are fully addressed.

1.1 The ongoing integration of AveXis into the Novartis quality system, including AveXis's adoption of the practices and requirements from the Novartis Global Operating Procedure, SOP 7039029, *GOP: Deviation Handling*, will be accelerated.

Target Completion Date (TCD): Ongoing

1.2 AveXis will adopt the practices and requirements from the Novartis Global Operating Procedure, SOP 7039029, *GOP: Deviation Handling*.

TCD: September 2019

1.3 AveXis will enhance the established non-conformance management process and the escalation process by aligning AveXis's process with relevant Novartis corporate procedures, including SOP 7038922, to ensure that, going forward, potential quality issues, including any issues relating to or potentially relating to the integrity of quality data generated at AveXis's sites, are timely escalated to senior quality leadership.

TCD: September 2019

1.4 AveXis will implement a certification process for investigators and QA approvers to ensure that all personnel handling investigation activities undergo focused training on root-cause analysis methodology and the use of investigation tools, including specific training on investigating and remediating data integrity and GDP anomalies, and demonstrate the ability to successfully perform their investigation and oversight responsibilities.

TCD: January 2020

1.5 As an interim control, AveXis will engage (b) (4) to provide independent oversight to the company's NC investigations, including review and approval of investigations.

TCD: Complete; (b) (4) protocol for reviewing NC investigations is under development

1.6 AveXis engaged (b) (4) to perform an independent, third-party data integrity investigation and assessment at AveXis pursuant to a written protocol.

TCD: Complete; (b) (4) data integrity investigation protocol is under development

1.7 Increase data integrity awareness through senior leadership engagement and site-wide communication efforts.

TCD: Ongoing

1.8 AveXis will re-train all employees engaged in GxP activities on POL-007, *Data Integrity Policy*, and SOP-003, *Good Documentation Practices*.

TCD: October 2019; additional training will be provided pursuant to the CAP

1.9 Establish and train AveXis personnel on the Novartis "SpeakUp" program with an emphasis on the importance of reporting concerns regarding potential misconduct or fraud

TCD: September 2019

1.10 Create a new Data Integrity Officer position reporting directly to AveXis's Head of QA and responsible for overseeing the implementation of the data integrity controls and oversight set forth in this response, and for ensuring the accuracy, completeness, and reliability of GxP data generated across AveXis's sites.

TCD: December 2019

1.11 Establish a mentorship program between AveXis quality personnel and Novartis data integrity and investigations subject matter experts (SMEs) to enhance skill building and instill best practices.

TCD: Ongoing

OBSERVATION 1(A)

There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has been already distributed.

A. Non-conformance Report NCR-1922 (which was open at the time of the current inspection) was opened on 15 May 2019 due to a report that was made to the CQO (Chief Quality Officer) alleging that data derived from the AVXS-101 In-Vivo Relative Potency Assay Studies 1-10 may have been mismanaged or even potentially manipulated. Aside from evaluations of Studies 1-10 and a planned evaluation of toxicological studies under NCR-2018 there is no documentation in this NCR that an audit of all other potentially impacted data, studies, and reports was conducted or is planned to determine if there was evidence of data mismanagement or manipulation or a justification for not conducting or planning such an audit. Additionally, there is no documentation in NCR-1922 as to why the NCR was not opened until 15 May 2019 when the initial allegation is documented as having been reported on 14 March 2019.

Specific Response to Observation 1(A)

Please note that the investigation into the data manipulation allegations noted in Observation 1(A) was conducted with focus, diligence, and significant resources.[10] As explained above, upon learning of what was then an *allegation* of data manipulation, AveXis immediately launched an internal investigation on March 14, 2019, led by senior officials from AveXis HR, Quality, and Legal, which included the development of an investigation plan, gathering of materials, preparing the necessary *Upjohn* warnings, and additional investigative steps. AveXis personnel immediately contacted the individual who made the allegations, but were informed that the individual was unavailable until March 26, 2019. AveXis personnel pursued other initial investigational steps and the individual who reported the allegations was interviewed on March 26, 2019. After conducting the interview and completing a thorough review of the testing records described by the reporter, AveXis determined that the allegations merited further investigation and informed Novartis on March 28, 2019.

[10] As described in more detail in Section I, above, the investigation noted in Observation 1(A) involved a mouse potency assay—known as the *in vivo* relative potency assay (IVRPA)—for release and stability testing of clinical product. The IVRPA used SMNΔ7 mice to determine the relative potency of lots of AVXS-101 for clinical product release and stability testing. It is important to note that IVRPA has not been used for clinical product release purposes since June 2018, nearly a year before Zolgensma® was approved, and was never used for the release of commercial product. Rather, a different in vitro cell-based assay and new *in vivo* functionality assay were validated and included in the Zolgensma® BLA as the tests to be used to assess potency for commercial release and stability.

For this phase of the investigation, an external law firm was engaged to conduct an internal review of the allegations, on April 3, 2019. Because the allegations involved two founders who were still senior executives and fixtures at AveXis, and because the allegations involved data manipulation, this initial internal investigation was led by external counsel to ensure that key evidence was preserved, efficiently gathered, and made available for a thorough technical review without interference from the two implicated senior AveXis executives.

Moreover, the investigation was significantly drawn out due to the implicated senior executives' lack of cooperation and categorical denial of the allegations, which continues to this day. Significant resources were therefore required to review thousands of hand-written and electronic records concerning the life history of individual mice and comparison of those records to entries on hundreds of spreadsheets. To accomplish this, we estimate that more than 2,000 hours were spent collectively by the investigation team from the engagement of external counsel until the start of the non-conformance phase of the investigation. When discrepancies were identified, technical experts were required to assess the discrepancies to determine whether they had any impact on the results of the underlying IVRPA studies, batch release decisions, and clinical data that may have been generated through use of those batches. In each case, these technical reviews found that the data manipulation issues had no impact on patient safety or product efficacy or quality.

During this time, AveXis was actively engaged in the investigation and in monitoring the results of the investigation. The initial investigation and interviews demonstrated that the two senior AveXis executives alleged to have been responsible could not offer a credible explanation for revisions to and inconsistencies in the data, and they were placed on administrative leave on May 3, 2019 to ensure that they had no access to data, systems, or staff. These two senior AveXis executives were later terminated for cause on August 13, 2019.[11] As a reminder, this phase of the investigation took 39 working days.

Following the initial investigation's determination that the allegations were credible and merited continued investigation, as a second phase, a NC investigation was opened on May 8, 2019 to further investigate the issues, including conducting a comprehensive root-cause analysis, conducting a more detailed risk assessment, and developing and implementing corrective and preventive actions to address the data integrity issues. A non-conformance report—NCR-1922—was opened in AveXis's ACE document management system on May 15, 2019 to document the investigation activities. A team consisting of AveXis senior Quality leadership, AveXis San Diego Quality Assurance and Quality Control, and Novartis GxP Compliance conducted the NC investigation.

[11] As noted in the public statements of his counsel, one of these executives continues to deny any wrongdoing.

The NC investigation—which remains open—is focused on concerns relating to *in vivo* mouse studies 1-10, which implicated IVRPA data for four product lots: Lot NCHAAV95MN0613 stability data at the 3-month time point; Lot 600307 release data; Lot 600729 release data; and Lot 600539 release data. Three of these lots had been consumed or were expired, with all material in the remaining lot placed on an hold at the AveXis Libertyville, Illinois site as of May 5, 2019.

The NC investigation proceeded according to the following methodology:

- Review of all possible sources of data pertaining to the assays in question, such as GMP data sheets for the IVRPA, original records used in the management of animals (cage cards), spreadsheets created by employees to hold data and calculate results of the assays, and laboratory logbooks;

- Identification of possible data discrepancies;

- Determination of possible alternative values for reported relative potency for lots involved in studies implicated;

- Evaluation of clinical studies potentially impacted by data integrity allegations;

- Evaluation of regulatory impact;

- Interviews with staff and management; and

- Recalculation of the results and material impact assessments.

Comparative reviews of data sources and interviews have confirmed that there were multiple instances of discrepancies of data used for *in vivo* studies 1-10. In order to either verify existing values, or to determine data values with an increased level of reliability for studies 1-10, a protocol was developed to verify the raw data and to establish procedures for evaluating such discrepancies. Employing this new protocol, raw data were revised when primary records supported revision, potency was recalculated for the IVRPA studies 1-10, and the resulting values from these studies would be annotated as having reduced validity, and that these results should be reported to the appropriate regulatory agencies, which was subsequently done in a timely manner.

NCR-1922's impact assessment further found that despite the IVRPA data concerns, the original clinical conclusions were not in question given the overall technical assessment of all QC release testing, including the *in vitro* potency assay, and the consistent performance of AVXS-101 in the

clinical trials. Specifically, during the development of the product and prior to submission of the BLA, FDA previously raised concern regarding the variability of the *in vivo* data from studies 1-10 and requested clinical results from ongoing studies. FDA also requested *in vitro* relative potency data to support the clinical profile of Zolgensma®. Accordingly, while studies 1-10 were used in the development of the product, these data would not have been relied upon to reach any clinical determinations given this variability.

AveXis recognizes that a thorough data integrity investigation should extend to all other potentially impacted data, studies, and reports to determine if there was evidence of data mismanagement or manipulation. Thus, the interim NCR-1922 included a CAPA to engage a third-party to perform an audit of AveXis data integrity compliance and recommend additional CAPAs. Accordingly, as the next phase of the investigation, AveXis engaged (b) (4) an independent third-party cGMP consultant, to perform a thorough assessment of AveXis's data integrity controls and oversight, and to investigate the extent of the data integrity deficiencies noted in the 483 and the data manipulation issues previously reported to FDA. Further, AveXis has also engaged (b) (4) to perform a retrospective assessment of critical and major NCRs, which includes out-of-specification test results, to assess the adequacy of the site's investigations and determine whether any investigations should be re-opened under (b) (4) supervision and oversight. (b) (4) will also provide an independent review of GxP activities.

Further showing that the company understands a thorough (b) (4) investigation should extend to all other potentially impacted data, studies, and reports, AveXis notes that through this investigation, (b) (4)

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AveXis opened an additional NC investigation on (b) (4) to investigate this (b) (4) (documented in NCR-2018). Based on information obtained pursuant to the

investigation, AveXis concluded that (b) (4) [redacted]. Although AveXis's investigation was ongoing during the July/August inspection, AveXis provided a draft copy of NCR-2018 to the FDA investigators, who requested and retained a copy of the draft investigation report and related documentation. AveXis will (b) (4) [redacted]

AveXis takes seriously the responsibility to ensure the accuracy and reliability of the company's data and are actively working to strengthen practices and procedures for data management activities as well as identifying, investigating and remediating any non-conformances with company requirements.

In this regard, AveXis has initiated CAPA-777, which was reviewed by FDA investigators during the July 2019 Inspection. The CAPA includes performing an expanded data integrity investigation pursuant to a written protocol, *see* Exhibit 4, to fully assess the GxP activities impacted by both of the senior executives associated with data manipulation and to perform a risk-based assessment of those activities to determine whether any further investigation or review is required.

Observation 1(A) Corrective and Preventive Actions

In addition to the actions noted above in Section II, including the actions undertaken pursuant to the QIP and the Data Integrity Remediation Plan, AveXis will undertake the following actions to ensure that the issues specifically noted in Observation 1(A) are fully addressed.

1.12 AveXis has initiated CAPA-777 to perform an expanded data integrity investigation pursuant to a written protocol to fully assess the GxP activities impacted by both of the senior AveXis executives associated with data manipulation and to perform a risk-based assessment of those activities to determine whether any further investigation or review is required.

TCD: September 2019

OBERVATION 1(B)

There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has been already distributed.

B. Non-conformance Report NCR-409 was opened on 31 Jan 2018 and has an "Event Description" of "On 31Jan2018, during a historical data review of the potency results for Drug Product Lot 600156 per SOP-285, Determination of In Vivo Relative Potency for AVXS-101 Drug Product, it was discovered that the associated assay form (FORM-212) was not completed at the time of CoA generation and approval for Lot 600156...." During the inspection, the associated FORM-212 was reviewed and it was observed that the date/time stamps on the 4 page form are discrepant in that 3 of the 4 pages have a "Generated" date /time of "05 Jan 2018 09:44AM" and 1 page (page 2) has a "Generated" date/time of " 04 Jan 2018 09:39AM". There is no documentation in NCR-409 that this discrepancy was noticed or investigated. Additionally, current SOP-381 Version 2.0 entitled "Control of QC Test Forms" does not specifically require verification of consistent date/time stamps on each page of a test form during reconciliation of the form.

Specific Response to Observation 1(B)

AveXis recognizes the importance of control of quality documents. AveXis notes that prior to FDA's inspection, in July 2018, the company implemented SOP-381, *Control of QC Test Forms*, which includes enhanced controls for quality documents, including establishing a process for reconciliation of quality forms. As part of the QIP, AveXis, with the assistance of Novartis quality personnel, will perform a comprehensive review of document control practices, procedures, and systems. As appropriate, CAPAs will be generated to enhance AveXis Quality Assurance's control of quality documents.

With respect to NCR-409, AveXis will amend the investigation report with an analysis of the apparent form issuance discrepancy, including root cause determinations and impact assessment. At a minimum, AveXis will revise SOP-381, *Control of QC Test Forms*, to require verification of consistent time/date stamps during reconciliation of the form. In addition, AveXis will perform a review of all forms and procedures used to record and report GxP data in order to ensure consistent practices for issuance, time/date stamps, reconciliation, and data management verification.

With respect to the investigation, as described above, AveXis is implementing substantial enhancements to assure robust quality investigations including an investigation certification program. As an interim control, AveXis has engaged (b) (4) to independently review AveXis NCRs prior to closure. Further, AveXis will engage (b) (4) to perform a protocol-based

retrospective review of closed major and critical NCRs, and a statistically significant sample of closed minor NCRs to assure that adequate investigations were performed and scientifically justified conclusions reached. In the event that this review identifies material deficiencies in conclusion or impact, the specific investigation will be amended and subject to review by (b) (4)

Observation 1(B) Corrective and Preventive Actions

In addition to the actions noted above in Section II, including the actions undertaken pursuant to the QIP and the Data Integrity Remediation Plan, AveXis will undertake the following actions to ensure that the issues specifically noted in Observation 1(B) are fully addressed.

1.13 With respect to NCR-409, AveXis will amend the investigation report with an analysis of the apparent form issuance discrepancy, including root cause determinations and impact assessment.

TCD: October 2019

1.14 AveXis will revise SOP-381, *Control of QC Test Forms*, and SOP-076, *Issuance and General Use of Logbooks*, to require verification of consistent time/date stamps during reconciliation of the form.

TCD: September 2019

1.15 AveXis will perform a review of all forms and procedures used to record and report GxP data in order to ensure consistent practices for time/date stamps, reconciliation and for data management verification and authorization.

TCD: December 2019

1.16 AveXis engaged (b) (4) to perform a protocol-based retrospective review of closed major and critical NCRs, and a statistically significant sample of closed minor NCRs to assure that adequate investigations were performed and scientifically justified conclusions reached.

TCD: Complete; (b) (4) retrospective review protocol is under development

OBERVATION 1(C)

There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has been already distributed.

C. Non-conformance Report NCR-965 was opened on 23 Aug 2018 and has and "Event Description" of "On 23Aug 2018, during the review of 7SMA mouse database, it was discovered that there were discrepancies in the data that was used to calculate relative potency for AVXS-101 Drug Product. Lot 816836 had single mouse survival days recorded that were different from the actual value...." As documented in the investigation most of the discrepancies noted were discrepant by a single day which was attributed to ambiguity in SOP-285 "Determination of In-Vivo Relative Potency for AVXS-101 Drug Product" however in 4 cases discrepancies of greater than 1 day were noted (ranging from 2-19 days). There is no documentation in NCR-965 that these 4 cases were investigated further to determine a potential root cause.

Specific Response to Observation 1(C)

AveXis recognizes that unexplained discrepancies must be appropriately investigated, including root cause determination. AveXis notes that since the initiation of investigation noted in NCR-965, the company has made significant quality enhancements to the San Diego site's performance of *in vivo* relative potency assay, including the establishment of quality oversight during the testing of the *in vivo* functionality assay.

The investigation documented in NCR-965 was initiated on August 23, 2018, following a review of the Δ7SMA mouse database that found discrepancies in the data that was used to calculate relative potency for AVXS-101 Drug Product lot 816836, released in September 2017 based on relative potency results obtained under SOP-285, the IVRPA. Specifically, recorded single mouse survival days were determined to vary from actual survival days. The investigation determined that due to the survival calculation discrepancy, the reported relative potency value of (b) (4)% for lot 816836 should have been reported as (b) (4)%. The relevant specification for potency was (b) (4) %, therefore the investigation concluded that there was no impact on product quality or subject safety.

AveXis performed a comprehensive data review as part of the investigation into survival date discrepancies associated with SOP-285. The investigation found that (b) (4) out of (b) (4) test animals were associated with a (b) (4) survival-days discrepancy attributed to lack of clear instructions in the relevant procedures for counting the day of birth of a test animal in the survival days calculation, as well as failure of laboratory personnel to employ consistent counting methods. An additional (b) (4) calculations were found in which the survival days calculation discrepancies was (b) (4) . Specifically, the review found discrepancies of (b) (4)

days. The investigation found no impact on any of the associated batches, except with respect to above-described impact on the relative-potency calculation for lot 816836. A mouse from the relevant group that received Lot 816836 was associated with the (b) (4) day discrepancy, which contributed to the change in reported relative potency to (b) (4)% from (b) (4)%. At the time of the investigation, SOP-285 was no longer used for release or stability testing. Nonetheless, the procedure was updated to provide a clear process for calculating survival days in the event that it is used again, for example as part of testing during an investigation.

With respect to root cause determination, AveXis notes that NCR-1922 addressees the same data set as NCR-965 and the interim NCR-1922 identified data manipulation as the likely cause of the four referenced cases of data discrepancy that were greater than 1 day. AveXis will amend NCR-965 with a summary of those conclusions and related impact assessment.

In addition, to assure that there is no ambiguity in the current *in vivo* test method, AveXis will review, and as necessary revise, SOP-346, *In-vivo Functionality Test using a Single Dose AVXS-101 in SMNΔ7 Mouse Model*, to provide specific instruction on how to calculate survival days.

Observation 1(C) Corrective and Preventive Actions

In addition to the actions noted above in Section II, including the actions undertaken pursuant to the QIP and the Data Integrity Remediation Plan, AveXis will undertake the following actions to ensure that the issues specifically noted in Observation 1(C) are fully addressed.

1.17 AveXis will amend NCR-965 with a summary of the conclusions from NCR-1922, which addresses the same dataset and related impact assessment.

TCD: October 2019

1.18 To assure that there is no ambiguity in the current *in vivo* test method, AveXis will review, and as necessary revise, SOP-346, *In-vivo Functionality Test using a Single Dose AVXS-101 in SMNΔ7 Mouse Model*, to provide specific instruction on how to calculate survival days.

TCD: September 2019

OBERVATION 1(D)

There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has been already distributed.

D. Non-conformance Report NCR-1116 was opened on 15 Oct 2018 and has "Event Description" of "Inconsistencies were identified during the review and approval of the data previously reported within REC-1606 v1.0 'Mouse Survival Data: Results for In-vivo Relative Potency for AVXS-101 Drug Product'...." As documented in the investigation " ... During investigational review of the Quality Employee's process, it was determined that some of the early raw data results were initially communicated verbally from the... to the AveXis Quality Employee...." There is no documentation in NCR-1116 explaining why the Quality Employee accepted verbal communication of raw data without corresponding written documentation.

Specific Response to Observation 1(D)

AveXis understands that quality data should be appropriately recorded and maintained. As identified in NCR-1116, AveXis data management procedures in place at the time of the relevant events did not provide specific details on verbal communication of data. Current AveXis procedures controlling data management include controls to prevent the acceptance of verbal communication of raw data without written documentation. Specifically, SOP-003, *Good Documentation Practices*, incorporated ALCOA principles in version 2.0 effective October 6, 2017, and was further updated August 2019 to incorporate the definition of raw data recorded on paper or electronically.

In addition, Policy POL-007, *Data Integrity Policy*, was established in April 2017 and also incorporates ALCOA principles, including the definition of an original record as "Data as the file or format in which it was originally generated, preserving the integrity (accuracy, completeness, content and meaning) of the record, *e.g.*, original paper record of manual observation, or electronic raw data file from a computerized system." To ensure that relevant employees fully understand the importance of these controls, AveXis will re-train all personnel who handle GxP data on these established data management procedures.

More broadly, as outlined above in Section II, AveXis is implementing a Data Integrity Remediation Plan. One pillar of this plan is improving quality culture and improving data integrity awareness across the company. As part of the Data Integrity Remediation Plan, (b) (4) will investigate the scope of data integrity anomalies at AveXis. This will include improper documentation of quality data. (b) (4) will also evaluate AveXis's data integrity controls and oversight.

Observation 1(D) Corrective and Preventive Actions

In addition to the actions noted above in Section II, including the actions undertaken pursuant to the QIP and the Data Integrity Remediation Plan, AveXis will undertake the following actions to ensure that the issues specifically noted in Observation 1(D) are fully addressed.

1.19 AveXis revised SOP-003, *Good Documentation Practices*, to incorporate the definition of raw data recorded on paper or electronically.

TCD: Complete

Further, as noted above in the response to Observation 1:

1.8 AveXis will re-train all personnel engaged in GxP activities on POL-007, *Data Integrity Policy*, and SOP-003, *Good Documentation Practices*.

TCD: October 2019; additional training will be provided pursuant to the CAP

OBSERVATION 2

Laboratory records do not include complete data derived from all tests, examinations and assay necessary to assure compliance with established specifications and standards.

A. *Analytical Balance ID #:* (b) (4) *which is used to weigh mice handled under SOP-268 Version 2.0 entitled "Observation and Handling of Study Mice for AVXS-101 Potency Assay" does not have audit trail capability. These mice are used for SOP-346 Version 3.0 entitled "In-vivo Functionality Test using a Single Dose AVXS-101 in SMN7 Mouse Model".*

B. *Printouts for the weighing of mice are not made and included in the logbook where the weights are currently manually recorded. Analytical balance ID #:* (b) (4) *which is used to weigh the mice is capable of producing printouts of weighings; however printouts of mouse weights are not made and included with the data that is manually recorded in the logbook, that as an example can be seen in Logbook ID Number 000139 "AVXS-101 In-vivo Functionality" on FORM-339 "Weight and Survival Data for AVXS-101 Functionality Test". These mice are used for SOP-346 Version 3.0 entitled "In-vivo Functionality Test using a Single Dose AVXS-101 in SMNΔ7 Mouse Model".*

C. *The equipment number of the analytical balance which is used to weigh mice handled under SOP-268 Version 2.0 entitled "Observation and Handling of Study Mice for AVXS-101 Potency Assay" is not recorded in the logbook which, as an example can be seen in Logbook ID Number 000139 "AVXS-101 In-vivo Functionality". These mice are used for SOP-346 Version 3.0 entitled "In-vivo Functionality Test using a Single Dose AVXS-101 in SMNΔ7 Mouse Model".*

General Response to Observation 2

AveXis fully recognizes the importance of ensuring that laboratory records include complete data derived from all tests, examinations, and assays necessary to assure compliance with establish specifications and standards. Assuring the accuracy, completeness, and reliability of GxP data is a fundamental principle of data integrity and good documentation practice, and one that AveXis takes extremely seriously.

Indeed, as discussed with the FDA investigators during the July 2019 inspection and as outlined above in Section II, at the time of the inspection, AveXis had several controls in place to ensure the completeness, accuracy, and reliability of laboratory records. For example, computerized systems generating electronic data, including electronic laboratory data, are subject to the qualification and validation requirements set forth in SOP-279, *Computerized System Qualification and Validation*. *See* Exhibit 5. These requirements include the establishment of user requirements specifications, vendor audits and assessments, risk assessments, configuration

specifications, design qualifications, installation qualification, operational qualification, performance qualification, a traceability matrix, a validation plan summary report, operational manuals, training, and the establishment of administration procedures. These requirements ensure that GxP computerized systems perform as expected in accordance with predetermined specifications, user-defined requirements, and applicable FDA regulations, including 21 CFR Part 11. As such, these requirements also ensure that electronic records generated at AveXis, including laboratory records, are accurate, complete, and reliable.

More broadly, pursuant to Plan 313 Version 4.0, *AveXis Data Integrity Plan*, *see* Exhibit 3, AveXis is performing data integrity assessments of computerized systems used for GxP operations across the company, including laboratory computerized systems, for adherence to ALCOA data integrity principles and 21 CFR Part 11 compliance. Please note that these assessments commenced in January 2019. AveXis's assessment of computertized systems is focused on identifying gaps in the following areas:

- Physical Security and Logical Security
- User Access and Segregation of Roles
- Electronic Records and Electronic Signatures
- Periodic Reviews of Audit Trails and Access Rights
- Validation life cycle documentation
- Data Life Cycle and Data Management
- Data Modifications, Review, and Approval
- Procedures and Agreements

Gaps identified pursuant to these computerized system assessments—which are ongoing—are documented in controlled forms, and these gaps are being remediated pursuant to written remediation plans.

With respect to non-electronic (*i.e.*, paper) GxP records, SOP-003, *Good Documentation Practices*, attached at Exhibit 6, provides that:

- Falsification of records is strictly prohibited. Pursuant to SOP-003, falsification includes back dating or entering a future date; signing someone else's name; signing a document or record before the activity is performed; signing for, witnessing, or verifying a step without witnessing or verifying the activity; copying and/or pasting

scanned signatures for use as approval signatures; entering data/information not directly obtained, that did not occur, or that was not observed; entering data when testing was not performed, completed, or that is not reflective of the actual result obtained; and destroying or voiding original data or information without documenting such action.

- All data/information are to be recorded by the person who has performed the activity/task unless the document clearly indicates that information is being record by someone other than the performer AND the performer's signature is also present.

- All entries must be made at the time tasks are performed. Records must indicate the date and/or time tasks were performed/recorded as indicated by specification, procedure, or record format.

- Raw data must be retained in its entirety and original form, e.g. printouts of all attempts at system suitability (whether passing or not) OR all calibration attempts, including failures.

SOP-238, *Data Integrity Controls*, attached at Exhibit 7, further provides that all data generated at AveXis must be accurate, legible, contemporaneous, original, and attributable (ALCOA). SOP-238 also prohibits deleting, manipulating, or modifying GxP data.

Against this backdrop, please note that during the inspection, the FDA investigators spent more than one full inspection day evaluating AveXis's installation qualification, operational qualification, and performance qualification (collectively, the qualification package) for the computerized imaging equipment used to perform the *in vitro* relative potency assay, which, as detailed above, was developed by AveXis to address widely recognized issues of variability with the *in vivo* relative potency assay. The investigators also assessed AveXis's oversight and controls relative to the computerized imaging equipment, including audit trail capability, access controls, and user privileges. The investigators' review of AveXis's qualification package for the computerized imaging equipment used to perform the *in vitro* relative potency assay and AveXis's oversight and controls relative to this instrument did not result in any inspectional observations. The investigators also reviewed raw *in vitro* relative potency assay data generated using the computerized imaging equipment. Their review did not result in any inspectional observations.

This being said, with respect to the specific laboratory records noted in Observation 2—*i.e.*, mice weighing records—AveXis recognizes that 483 identifies areas where documentation practices relating to mice weighing could be strengthened. The company also recognizes that the recently identified data manipulation relating to mice weighing records and SOP-285—which AveXis reported to FDA on June 28, 2019—is a serious issue. Indeed, as FDA is aware, upon learning of this alleged data manipulation, AveXis performed an internal investigation to assess the

veracity of the claims and to determine the potential scope of the data inaccuracies. AveXis engaged an independent third party to interview key personnel regarding the data manipulation, including laboratory and vivarium personnel, and to perform a comprehensive review of all available records relating to SOP-285.

While AveXis believes, based on this initial investigation, that there are no systemic or widespread data integrity or document management deficiencies at the company, AveXis has engaged (b) (4) to perform a data integrity assessment of the company's manufacturing, laboratory, and clinical data. In light of the 483, the scope of (b) (4) assessment has been expanded to cover the company's data integrity controls and oversight more broadly, including documentation practice controls; controls relating to the issuance of controlled forms and documents; the site's computerized systems controls; processes for reviewing data pursuant to release, including the scope of QA review of electronic and paper records; and AveXis's internal audit function.

In addition to assessing AveXis's data integrity controls and oversight, (b) (4) will investigate whether the scope of the data integrity deficiencies is limited to the specific instances previously reported to FDA and whether the scope of the documentation deficiencies is limited to the specific instances noted in the 483. Pursuant to this investigation, (b) (4) will evaluate raw data, including laboratory data submitted to FDA in the Zolgensma® BLA, for evidence of discrepancies or manipulation.

AveXis also recognizes that Observation 2 identifies areas where the company's controls and oversight to ensure the completeness, accuracy, and reliability of GxP records, including laboratory records, could be further strengthened, particularly respect to records that, historically, have not been classified as electronic records. In this regard, as detailed above in the section setting forth the CAP, AveXis is implementing a Data Integrity Remediation Plan to ensure that the 483 observations are comprehensively addressed and to prevent recurrence of such issues in the future. CAPAs relating to the specific instances noted in Observation 2 are detailed below.

Observation 2 Corrective and Preventive Actions

In addition to the actions noted above in Section II, including the actions undertaken pursuant to the QIP and the Data Integrity Remediation Plan, AveXis will undertake the following actions to ensure that the issues specifically noted in Observation 2 are fully addressed.

2.1 AveXis engaged (b) (4) to perform an independent, third-party data integrity investigation and assessment at AveXis pursuant to a written protocol.

TCD: Complete; (b) (4) data integrity investigation protocol is under development

OBSERVATION 2(A)

Laboratory records do not include complete data derived from all tests, examinations and assay necessary to assure compliance with established specifications and standards.

A. *Analytical Balance ID #:* (b) (4) *which is used to weigh mice handled under SOP-268 Version 2.0 entitled "Observation and Handling of Study Mice for AVXS-101 Potency Assay" does not have audit trail capability. These mice are used for SOP-346 Version 3.0 entitled "In-vivo Functionality Test using a Single Dose AVXS-101 in SMN7 Mouse Model".*

Specific Response to Observation 2(A)

As outlined above, AveXis has established several procedural controls to ensure that electronic records, including laboratory records, are accurate, complete, and reliable. Because the analytical balance noted in Observation 2(A) (Equipment ID No. (b) (4)) does not generate electronic records and, further, because this particular analytical balance was located in the R&D area and used historically for R&D purposes, it was not subject to these robust procedural controls.

In light of the investigators' observation regarding the audit trail capability of Analytical Balance ID No. (b) (4) , AveXis will initiate a change control to update or replace this analytical balance with a weighing solution with audit trail capability. AveXis is currently evaluating two options—one where the existing analytical balance is connected to a server using Mettler Toledo's LabX® laboratory data management software and another where AveXis will replace Equipment ID No. (b) (4) with an audit-trail enabled weighing solution.

As an interim control, AveXis will ensure that the print function for Analytical Balance ID No. (b) (4) is enabled and that weight slips are automatically generated every time the balance is used, either for weight check, calibration, or official testing purposes. To ensure full traceability of the weighing results, these printouts will include a balance identifier in the header of the printout, a unique sequence number, and a date and time stamp. These printouts will be included in the official testing records, and will be initialed by the operator at the end of each session.

AveXis will also revise SOP-066, *Operation of QC Balances*, to state that every use of the analytical balance must be recorded in the analytical balance logbook. In addition, pending the introduction of the enhanced weighing solution noted above, AveXis will introduce second person verification for all mouse weighing activities performed pursuant to SOP-268 to ensure that the data recorded in the testing records are complete, accurate, and reliable. The individual responsible for performing second person verification will document their review in the

analytical balance logbook and testing records, including their name and the date and time they witnessed and verified the weighing activities.

AveXis will also revise SOP-268, *Observation and Handling of Study Mice for AVXS-101 Potency Assay*, and related FORM-339, to state that printouts related to weighing performed in the vivarium must be reviewed and verified against the analytical balance logbooks to ensure that the data between the balance printout and the logbooks, including date of analysis, time of analysis, analyst name, and equipment number, are consistent.

More broadly, AveXis will conduct a company-wide data integrity and documentation practice gap assessment for equipment used to perform quality control testing. This gap assessment will evaluate analytical balances used for GxP operations, including any analytical balances used for mice weighing activities, to determine whether such balances comply with FDA's and AveXis's data integrity expectations. Any equipment that does not meet FDA's data integrity expectations will be upgraded, and any equipment that cannot be upgraded will be replaced. In each case, AveXis will implement second person verification, as outlined above, as an interim control to ensure data accuracy, reliability, and completeness.

Additionally, while the company believes that the data inaccuracies relating to mice weighing are limited to the specific instances reported to FDA on June 28, 2019, AveXis has engaged (b) (4) to perform a data integrity assessment. As detailed above, this assessment will cover AveXis's data integrity controls and oversight as well as data submitted to FDA in the Zolgensma® BLA.

Observation 2(A) Corrective and Preventive Actions

In addition to the actions noted above in Section II, including the actions undertaken pursuant to the QIP and the Data Integrity Remediation Plan, AveXis will undertake the following actions to ensure that the issues specifically noted in Observation 2(A) are fully addressed.

2.2 AveXis will update or replace Analytical Balance ID No. (b) (4) with a weighing solution with audit trail capability.

TCD: December 2019

2.3 As an interim control, AveXis will ensure that the print function for Analytical Balance ID No. (b) (4) is enabled and that weight slips are automatically generated every time the balance is used, either for weight check, calibration, or official testing purposes.

TCD: September 2019

2.4 AveXis will revise SOP-066, *Operation of QC Balances*, to state that every use of the analytical balance must be recorded in the analytical balance logbook.

TCD: September 2019

2.5 AveXis will introduce second person verification for all mouse weighing activities performed pursuant to SOP-268 to ensure that the data recorded in the testing records are complete, accurate, and reliable.

TCD: September 2019

2.6 AveXis will revise SOP-268, *Observation and Handling of Study Mice for AVXS-101 Potency Assay*, and related FORM-339, to state that printouts related to weighings performed in the vivarium must be reviewed and verified against the analytical balance logbooks to ensure that the data between the balance printout and the logbooks, including date of analysis, time of analysis, analyst name, and equipment number, are consistent.

TCD: November 2019

2.7 AveXis will conduct a company-wide data integrity and documentation practice gap assessment for equipment used to perform quality control testing.

TCD: December 2019

OBSERVATION 2(B)

Laboratory records do not include complete data derived from all tests, examinations and assay necessary to assure compliance with established specifications and standards.

B. Printouts for the weighing of mice are not made and included in the logbook where the weights are currently manually recorded. Analytical balance ID #: (b) (4) *which is used to weigh the mice is capable of producing printouts of weighings; however printouts of mouse weights are not made and included with the data that is manually recorded in the logbook, that as an example can be seen in Logbook ID Number 000139 "AVXS-101 In-vivo Functionality" on FORM-339 "Weight and Survival Data for AVXS-101 Functionality Test". These mice are used for SOP-346 Version 3.0 entitled "In-vivo Functionality Test using a Single Dose AVXS-101 in SMNΔ7 Mouse Model".*

Specific Response to Observation 2(B)

AveXis understands the importance of ensuring that original raw data, such as analytical balance printouts, are included in laboratory records and available for review throughout the applicable record retention period. With respect to the mice weighing records noted in Observation 2(B), AveXis recognizes that the original raw data relating to the mice weighing for SOP-346, *In-vivo Functionality Test using a Single Dose AVXS-101 in SMNΔ7 Mouse Model*—i.e., the balance sheet printouts—should have been included in the testing records subject to quality review.

In light of the investigators' observation, AveXis will revise SOP-268, *Observation and Handling of Study Mice for AVXS-101 Potency Assay*, and related FORM-339 to state that that analysts must generate balance printouts for every use of the analytical balance, including weight checks, calibrations, and mice weighing, and that the balance printouts must include a unique sequence number and a date and time stamp. The analysts will be required to write their initials and individual mouse ID on the printout to assure full traceability.

Revised SOP-268 will also require second person verification for all mouse weighing activities performed pursuant to SOP-268 to ensure that the data recorded in the testing records are complete, accurate, and reliable. The individual responsible for performing second person verification will document their review in the analytical balance logbook and testing records, including their name and the date and time they witnessed and verified the weighing activities.

AveXis believes that these additional controls will ensure the accuracy, reliability, and completeness of mice weighing data.

Additionally, as detailed above, while the company believes that the data inaccuracies relating to mice weighing are limited to the specific instances reported to FDA on June 28, 2019, AveXis has engaged (b) (4) to perform a data integrity assessment. This assessment will cover

AveXis's data integrity controls and oversight at the San Diego site, as well as manufacturing, laboratory, and clinical data submitted to FDA in the Zolgensma® BLA. (b) (4) will also be performing assessments across the AveXis sites, including with respect to the company's commercial manufacturing, laboratory, and clinical data.

Observation 2(B) Corrective and Preventive Actions

In addition to the actions noted above in Section II, including the actions undertaken pursuant to the QIP and the Data Integrity Remediation Plan, AveXis will undertake the following actions to ensure that the issues specifically noted in Observation 2(B) are fully addressed.

As noted above in the response to Observation 2:

2.3 AveXis will ensure that the print function for Analytical Balance ID No. (b) (4) is enabled and that weight slips are automatically generated every time the balance is used, either for weight check, calibration, or official testing purposes.

TCD: September 2019

2.4 AveXis will revise SOP-066, *Operation of QC Balances*, to state that every use of the analytical balance must be recorded in the analytical balance logbook.

TCD: September 2019

2.5 AveXis will introduce second person verification for all mouse weighing activities performed pursuant to SOP-268 to ensure that the data recorded in the testing records are complete, accurate, and reliable.

TCD: September 2019

2.6 AveXis will revise SOP-268, *Observation and Handling of Study Mice for AVXS-101 Potency Assay*, and related FORM-339, to state that printouts related to weighings performed in the vivarium must be reviewed and verified against the analytical balance logbooks to ensure that the data between the balance printout and the logbooks, including date of analysis, time of analysis, analyst name, and equipment number, are consistent.

TCD: November 2019

OBSERVATION 2(C)

Laboratory records do not include complete data derived from all tests, examinations and assay necessary to assure compliance with established specifications and standards.

C. The equipment number of the analytical balance which is used to weigh mice handled under SOP-268 Version 2.0 entitled "Observation and Handling of Study Mice for AVXS-101 Potency Assay" is not recorded in the logbook which, as an example can be seen in Logbook ID Number 000139 "AVXS-101 In-vivo Functionality". These mice are used for SOP-346 Version 3.0 entitled "In-vivo Functionality Test using a Single Dose AVXS-101 in SMNΔ7 Mouse Model".

Specific Response to Observation 2(C)

AveXis understands the importance developing and implementing sufficient controls and oversight to ensure the traceability of GxP data. This includes ensuring that GxP records appropriately identify each piece of equipment used to perform the activities documented in such records. In light of the investigators' observation relating to documentation of the analytical balance identification number in the corresponding testing logbooks, AveXis recognizes that including this information in the testing logbooks would enhance traceability. Accordingly, AveXis will revise FORM-339 to require the documentation of the balance ID in testing logbooks.

More broadly, AveXis will conduct a review of logbooks and accompanying procedures to ensure that all logbooks used to document GxP activities require documentation of the equipment used to perform the GxP activities documented in such logbooks.

Observation 2(C) Corrective and Preventive Actions

In addition to the actions noted above in Section II, including the actions undertaken pursuant to the QIP and the Data Integrity Remediation Plan, AveXis will undertake the following actions to ensure that the issues specifically noted in Observation 2(C) are fully addressed.

2.8 AveXis will revise FORM-339 to require the documentation of the balance ID in testing logbooks.

TCD: September 2019

2.9 AveXis will conduct a review of logbooks and accompanying procedures to ensure that all logbooks used to document GxP activities require documentation of the equipment used to perform the GxP activities documented in such logbooks.

TCD: December 2019

OBSERVATION 3

The responsibilities and procedures applicable to the quality control unit are not fully followed.

Specifically, vivarium employees who have responsibilities for GMP functions such as animal dosing, tail snips for genotyping, weighing, death determination, and contemporaneous documentation report directly to an R&D manager. This is not in accordance with the "Quality Manual" version 3. There are (b) (4) *employees that perform these functions for commercial product testing (SOP-346 - In-vivo Functionality Test using a Single Dose AVXS-101 in SMN 7 Mouse Model) who directly report and are supervised by a "Senior Scientist" in the Research and Development team. This Senior Scientist has self- described no direct prior experience in GMP controlled lab work.*

Response to Observation 3

AveXis recognizes the importance of a strong, independent quality unit at the San Diego site. The company further understands that the quality unit's responsibilities and procedures must be in writing and must be followed. Accordingly, the company has in place a Global Quality Policy, Corporate Quality Manual, and the site-specific, San Diego Supporting Documentation (Quality Manual), which collectively establish the San Diego site quality unit's responsibilities.

AveXis has invested significant resources to strengthen its quality systems and to ensure sustainable compliance. AveXis notes that the San Diego site research and development personnel currently performing *in vivo* assays under GxP received training on AveXis's good documentation practice procedure and data integrity policy in March 2018. As described in the response to Observation 1, above, until May 2018, the San Diego site functioned solely as a research and development facility, with limited quality oversight. The research and development personnel received additional classroom-based training on good documentation practice in November-December 2018. In addition, in January 2019, AveXis created a training curriculum for *in vivo* testing, including for the relevant research and development personnel. This curriculum will be reviewed by Novartis SMEs and updated, as required.

Nonetheless, to further strengthen site practices, AveXis commits to transferring or hiring employees within the Quality organization dedicated to and solely responsible for performing *in vivo* testing. As an interim measure until such personnel are in place, an analyst within the Quality organization will provide second person review and contemporaneous verification of GxP *in vivo* testing operations performed by research and development personnel at the San Diego facility. AveXis notes that since October 2018 all data generated for the *in vivo* functionality assay has been reviewed by the Quality organization in accordance with SOP-087, *QC Laboratory Documentation*. This includes all commercially released batches.

In addition, AveXis notes that as described above, organizational assessments of AveXis's quality unit will be performed to align with Novartis's quality structure. The assessment will include a review of personnel assignments, reporting structures, training, and experience. A separate organizational assessment will be performed by (b) (4) to assess the effectiveness and capabilities of the AveXis quality organization from a resources and staffing perspective.

In addition, AveXis will perform a comprehensive review of responsibility for all activities related to the operation of the vivarium and to the management of the SMNΔ7 mice. AveXis notes that a third-party, (b) (4), manages the vivarium. (b) (4) personnel perform daily animal health checks (food, water, bedding, etc.), which currently includes documentation and notification when an animal is found missing or deceased. (b) (4) is managed by AveXis's Supplier Quality program and was audited prior to being qualified as a supplier. Regardless of affiliation or reporting structure, all vivarium personnel engaged in GxP activities have appropriate training and experience to fulfill their responsibilities and, as described above, AveXis will implement additional quality oversight enhancements.

Further, with respect to (b) (4), AveXis recognizes the opportunity to enhance its supplier oversight. AveXis will perform a review of responsibility for all activities related to the operation of the vivarium and to the management of the SMNΔ7 mice. Based on the review, enhancements will be implemented, including, as appropriate, transfer of GxP responsibilities from (b) (4) to AveXis personnel. In addition, Novartis SMEs will review the AveXis Supplier Quality program to ensure appropriate oversight of all qualified suppliers.

Observation 3 Corrective and Preventive Actions

In addition to the actions noted above in Section II, including the actions undertaken pursuant to the QIP and the Data Integrity Remediation Plan, AveXis will undertake the following actions to ensure that the issues specifically noted in Observation 3 are fully addressed.

3.1 AveXis will assess the current training curriculum for personnel performing *in vivo* assay testing.

TCD: November 2019

3.2 AveXis will transfer or hire employees within the Quality organization dedicated to and solely responsible for performing *in vivo* testing.

TCD: Ongoing; position posted and candidate identification in-progress

3.3 As an interim measure until such personnel are in place, an analyst within the AveXis Quality organization will provide second person review and contemporaneous verification of GxP *in vivo* QC testing operations performed by research and development personnel at the San Diego facility.

TCD: September 2019

3.4 AveXis will perform a review of responsibility for all activities related to the operation of the vivarium and to the management of the SMNΔ7 mice. Based on the review, enhancements will be implemented, including, as appropriate, transfer of GxP responsibilities from (b) (4) to AveXis personnel.

TCD: October 2019

3.5 As part of the QIP, organizational assessments of AveXis's quality unit will be performed to align with Novartis's quality structure, including personnel assignments, reporting structures, training, and experience.

TCD: Ongoing

3.6 AveXis engaged (b) (4) to assess the effectiveness and capabilities of the AveXis quality organization from a resources and staffing perspective.

TCD: Complete; (b) (4) protocol for assessing the effectiveness and capabilities of AveXis's quality organization is under development

3.7 As part of the QIP, Novartis SMEs will review the AveXis Supplier Quality program to ensure appropriate oversight of all qualified suppliers.

TCD: Ongoing

OBSERVATION 4

Laboratory records do not include complete records of any testing and standardization of laboratory reference standards.

Specifically, reference standard lots have not been tested and shown to meet initial release criteria in applicable versions of SOP-285 (Determination of ln Vivo Relative Potency for AVXS-101 Drug Product) such as minimum slope of increasing doses, minimum mouse cohort sizes, and minimum survivability medians at the test dose.

This is applicable to reference standard Lots #AAV9SMN0613 (NCH) and #600443 (RS-002) tested in March 2017 and February 2018 respectively which serve as reference standards for potency and in-vivo functionality methods performed for the AVXS-101 product over the past three years. These lots have potency values reported in BLA 125694.

Response to Observation 4

As described in detail above, *in vivo* relative potency testing was initially performed under SOP-285, *Determination of ln Vivo Relative Potency for AVXS-101 Drug Product*. In June 2018, at FDA's request, SOP-285, was replaced by the SOP-347, *Determination of In-vitro Relative Potency for AVXS-101 Drug Substance and Drug Product* and SOP-346, *In-vivo Functionality Test using a Single Dose AVXS-101 in SMNΔ7 Mouse Model.* SOP-347 and SOP-346 are the approved methods included in BLA 125694 and the commercial AVXS-101 Drug Product release specification.

With respect to the reference standard lots referenced in 483 Observation 4, Lot AAV9SMN0613 was established as the initial reference standard for SOP-285 testing following assay development and subsequently used for all SOP-285 testing. Lot AAV9SMN0613 has not been used as a reference standard for SOP-347. Lot 600443 was released under SOP-285 and selected as a reference standard for SOP-347 method validation studies. During the method validation studies, AVXS-101 drug product lot-to-lot consistency was evaluated for lots tested per SOP-347 using Lot 600443 as a reference standard. The suitability of Lot 600443 for use as a reference standard for SOP-347 testing is supported by the observed consistency in potency from lot to lot.

AveXis notes that since the qualification of lots AAV9SMN0613 and 600443 as reference standards, the company has revised SOP-330 *Reference Standard Qualification Procedure*, including adding a process for assignment of potency for a new reference standard through comparison to the current reference standard. AveXis notes that the revised qualification procedure was reviewed by FDA investigators during the July 2019 inspection and resulted in no observations.

During FDA's July 2019 inspection, it was found that in initial testing, lots AAV9SMN0613 and 600443 did not meet all relevant acceptance criteria in the applicable version of SOP-285.

Lot AAV9SMN0613 testing was performed during the initial assay development for SOP-285. Due to a rounding error, AveXis erroneously concluded that the testing met the assay acceptance criteria of (b) (4) for the slope of the dose response curve. As identified during the July 2019 inspection, absent the rounding error, the assay test should have been considered invalid and retesting performed. AveXis notes that the rounding error was unrelated to product specification acceptance criteria. AveXis notes that site procedures for rounding are currently described in SOP-003, *Good Documentation* Practices. But in light of the investigators' observation, AveXis will develop and implement a separate SOP specifically for significant figures and rounding.

AveXis further notes that *in vitro* testing of Lot AAV9SMN0613 was performed under SOP-347 as part of the bridging study ((b) (4)) for the BLA 125694 Late-Cycle Review Response. Testing using the validated *in vitro* method was within acceptance criteria, resulting in a within-specification relative potency value of (b) (4) %.

As noted, Lot AAV9SMN0613 was used as a reference standard for lots released under SOP-285. All lots tested under SOP-285 with lot AAV9SMN0613 as the reference standard have subsequently been tested under SOP-347 during stability testing, side-by-side comparability ((b) (4)) or as a result of CAPAs related to NCR-1922. The results for all such lots were within the AVXS-101 release specification of (b) (4) % relative potency. As described above, the *in vitro* method is considered more reliable than the SOP-285 method, and was developed and validated at the request of FDA.

For release testing of Lot 600443, performed under SOP-285, the assay acceptance criteria for the reference standard dose response curve and the mouse cohort size of (b) (4) mice were not met following the removal of data determined to be unreliable as part of the investigation documented in NCR-1922. AveXis notes that the investigation confirmed that there was no impact on drug product lots released using lot 600443 as a reference standard. Further, *in vitro* testing of lot 600443 during the method validation for SOP-347 resulted in a within-specification relative potency value of (b) (4) %.

In addition to the *in vitro* testing already performed, to further assure the suitability of the impacted reference standard lots, AveXis will retest lots AAV9SMN0613 and 600443, under the *in vivo* functionality method, SOP-346, the approved *in vivo* method in BLA 125694. In addition, AveXis will revise BLA 125694 to remove the IVRPA results reported for lots

AAV9SMN0613 and 600443 and instead report the data generated for each lot under SOP-347 and SOP-346.

Observation 4 Corrective and Preventive Action

In addition to the actions noted above in Section II, including the actions undertaken pursuant to the QIP and the Data Integrity Remediation Plan, AveXis will undertake the following actions to ensure that the issues specifically noted in Observation 4 are fully addressed.

4.1 AveXis will develop and implement a separate SOP specifically for significant figures and rounding.

TCD: November 2019

4.2 AveXis will retest Lot AAV9SMN0613 and Lot 600443, per the *in vivo* functionality method (SOP-346), the approved method in BLA 125694.

TCD: December 2019

4.3 AveXis will revise BLA 125694 to include the *in vivo* functionality test data generated for Lot AAV9SMN0613 and Lot 600443.

TCD: March 2020

OBSERVATION 5

Established test procedures are not followed.

Specifically, as per SOP-346 Version 3.0 "In- vivo Functionality Test using a Single Dose AVXS-101 in SMN 7 Mouse Model" the mouse date of death is in part defined as the " ... date the animal first lost (b) (4) % of its body weight...". As per SOP-268 Version 2.0 "Observation and Handling of Study Mice for AVXS-101 Potency Assay" study animals are weighed "...(b) (4) (b) (4) (separated by at least (b) (4)) until end of study... " AveXis has interpreted the date the animal first lost (b) (4) % of its body weight as the date this loss is first documented. Since mice are not weighed daily there is no documentation showing the exact date the mouse lost (b) (4) % of its body weight.

Response to Observation 5

AveXis understands the importance of following established test procedures, and that testing activities should be documented at the time of performance. With respect to the test procedures noted in Observation 5, SOP-346 Version 3.0, *In-vivo Functionality Test using a Single Dose AVXS-101 in SMNΔ7 Mouse Model*, and SOP-268 Version 2.0, *Observation and Handling of Study Mice for AVXS-101 Potency Assay*, the observation correctly notes these test procedures state that study mice should be weighed (b) (4) , separated by at least (b) (4) , and that, for study mice dosed with AVXS-101, the date on which an animal first loses (b) (4) % or more of its body weight is one of the methods used by AveXis to determine mouse date of death. The other method, the actual death of a study mouse, was assessed(b) (4)pursuant to health checks performed by laboratory personnel.

With regard to the frequency of mouse weighing, as discussed with the FDA investigators during the inspection, AveXis selected (b) (4) , separated by at least (b) (4) to, among other reasons, minimize disruptions to the study mice, as the stress associated with handling could affect survival. As noted in the 483, this frequency—(b) (4) separated by at least (b) (4) (b) (4)—is the frequency that analysts actually performed study mice weighing—*i.e.*, analysts followed these established test procedures.

AveXis also understands FDA's concern that due to the passage of time between weighings—at least (b) (4) —there is a possibility a study mouse could exceed the (b) (4) % weight loss threshold without detection for (b) (4) . Accordingly, following the inspection, AveXis initiated a retrospective review of all commercial lots of AVXS-101 (Zolgensma®) tested using SOP 346, with a focus on study mice that were declared dead due to losing (b) (4) % or more of their body weight. As FDA is aware, the release specification for the *in vivo* functionality test (SOP 346) is a median survival of (b) (4) days or greater. Accordingly, AveXis investigated whether any median test article study mice that had been declared dead based on (b) (4) % weight loss had been so declared on or after day (b) (4) ensuring that study mice who lost (b) (4) % or more of their body weight

on days (b) (4) would be flagged for further investigation and impact assessment. AveXis's retrospective review, summarized in the memorandum attached at Exhibit 8, confirmed that no study mice at median survival were declared dead based on (b) (4)% weight loss except Lot 601537, for which (b) (4)% weight loss was detected on day (b) (4) Since the weight loss did not exceed (b) (4)% as recorded on day (b) (4) the median survival for Lot 601537 was at minimum (b) (4)days, within the release specification.

Please note that any additional handling of mice could be quite stressful (especially for the dam) and could affect survival. Accordingly, and in light of the FDA investigators' observation, AveXis will review and revise, as necessary, SOP 346, *In-vivo Functionality Test using a Single Dose AVXS-101 in SMNΔ7 Mouse Model*, SOP 268, *Observation and Handling of Study Mice for AVXS-101 Potency Assay*, and related Form 339 to evaluate whether study mice should be weighed (b) (4) throughout the study period.

Observation 5 Corrective and Preventive Action

In addition to the actions noted above in Section II, including the actions undertaken pursuant to the QIP and the Data Integrity Remediation Plan, AveXis will undertake the following actions to ensure that the issues specifically noted in Observation 5 are fully addressed.

5.1 AveXis initiated a retrospective review of all commercial lots of AVXS-101 (Zolgensma®) tested using SOP 346 with a focus on study mice that were declared dead due to losing (b) (4)% or more of their body weight.

TCD: Complete

5.2 AveXis will review and revise as necessary SOP 346, *In-vivo Functionality Test using a Single Dose AVXS-101 in SMNΔ7 Mouse Model*, SOP 268, *Observation and Handling of Study Mice for AVXS-101 Potency Assay*, and related Form 339 to evaluate whether study mice should be weighed (b) (4) throughout the study period.

TCD: November 2019