MEMORANDUM

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FDA / CBER / OTAT

BLA 125694	
BLA Submission date	October 1, 2018
BLA Approval date	May 24, 2019
Incident report	June 28, 2019
Memo date	July 26, 2019
Applicant	AveXis, Inc.
Product / Trade Name	onasemnogene abeparvovec-xioi / Zolgensma
Indication	Treatment of pediatric patients less than 2 years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the *survival motor neuron 1* (*SMN1*) gene

Background

On May 24, 2019, the FDA approved the Biologics License Application (BLA) for onasemnogene abeparvovec-xioi (Zolgensma) to treat pediatric patients less than 2 years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene. On June 28, 2019, the product manufacturer (AveXis, Inc.) called Andrew Byrnes, PhD, CMC (Chemistry, Manufacturing, and Controls) reviewer for the BLA and notified him that AveXis personnel had manipulated data from an in vivo murine potency assay (SOP-285). On June 28, 2019, AveXis submitted a report of their investigation of that data manipulation to both the IND (15699) and BLA. On July 1, 2019, Dr. Byrnes informed members of the BLA review team and managers in the Office of Tissues and Advanced Therapies (CBER/OTAT) and the Office of Compliance and Biologics Quality (CBER/OCBQ) of the AveXis investigation report. At that time, Dr. Byrnes expressed his preliminary concerns regarding the data manipulation and its potential impact on the reliability and accuracy of the FDA reviews of the BLA, and its potential impact on the marketed product. The concerns expressed by Dr. Byrnes were considered during subsequent discussions of the BLA review team and OTAT and OCBQ management.

On July 8, 11, and 19, 2019, the BLA review team discussed the implications of the data manipulation. Those discussions included representatives from the project management, CMC, pharmacology/toxicology, clinical, and OCBQ teams who had reviewed the original BLA, and management from both OCBQ and OTAT. I have reviewed the AveXis report and participated in the internal discussions by the BLA review team and management on July 8, 11, and 19, 2019. I have considered the concerns expressed by members of the BLA review team as well as OTAT and OCBQ management. The purpose of this memorandum is to provide my current assessment of the implications of this event of data manipulation on the regulatory status of the BLA and the marketed product.

Summary

As noted, AveXis submitted some manipulated data in the original BLA. During the BLA review, the FDA used this information to evaluate product comparability and nonclinical (animal) pharmacology. As a result, some sections of several of the original BLA reviews may not be reliable and accurate. While the data manipulation directly involves CMC information, there are implications for the BLA reviews by several disciplines, including CMC, pharmacology/toxicology, statistics, and clinical. I have no reason to believe that any data, other than the data described in the AveXis investigation report, were manipulated. Particularly, I am aware of no evidence that patient clinical data were manipulated.

The product that was administered in the Phase 1 clinical trial and some of the nonclinical pharmacology studies was manufactured by a different process than the product that was administered in the Phase 3 clinical trial and the animal toxicology studies. Because the manufacturing processes were different, interpretation of the overall clinical trial and nonclinical study results depends on understanding the characteristics of the Phase 1 version of the product in relationship to the characteristics of the Phase 3 version of the product. The data that were manipulated involve the results of an assay (SOP-285) that was critical in characterizing the comparability between the two versions of the product. The data manipulation seems likely to impact the interpretation of the Phase 1 clinical trial results, as well as the interpretation of the results of some, but not all, of the nonclinical studies in the original BLA. At this time, the data manipulation does not appear to impact the interpretation of the results of the animal toxicology studies or the Phase 3 clinical trial.

Based on the information available at this time, the Phase 3 clinical trial results continue to provide compelling evidence of the effectiveness of Zolgensma, along with sufficient evidence of safety to support an overall favorable benefit-risk profile. Due to the data manipulation, the comparability of the version of the product administered in the Phase 1 clinical trial to the version of the product administered in the Phase 3 clinical trial is uncertain. However, both the Phase 1 version of the product and the Phase 3 version of the product consist of the same vector and transgene; therefore, the two versions of the product are closely related. Therefore, my current assessment is that the Phase 1 trial results provide supportive (confirmatory) evidence of the effectiveness of the Phase 3 product. The BLA meets the regulatory requirement for substantial evidence of effectiveness, based on one adequate and well-controlled investigation (i.e., the results of the Phase 3 trial) plus supportive evidence (i.e., the results of the Phase 1 trial). Based on the information currently available, Zolgensma is safe, pure, and potent (effective) for the indicated population.

A potency assay measures the therapeutic activity of a product. Thus, the results of a potency assay describe the activity of a product, and can be used to assess whether two versions of a product have similar activity. Based on the available data, it appears that the results of the SOP-285 in vivo murine potency assay were manipulated and are not reliable. However, SOP-285 is not used for release of lots of the currently marketed product. Rather, lot release for Zolgensma considers the results of two other potency assays: SOP-346, an in vivo murine potency assay that replaced SOP-285 during clinical development; and SOP-347, an in vitro potency assay which is less variable than either of the in vivo potency assays. The AveXis report does not indicate that any of the data manipulation involved the results of SOP-346 or SOP-347. Based on my discussions

with the BLA review team, and pending the results of further investigation, including an inspection of the AveXis testing site(s), the results of the SOP-346 and SOP-347 potency assays remain suitable for lot release of Zolgensma.

A complete assessment of the impact of the data manipulation will require additional investigation, discussions both internally within CBER and with AveXis, will probably require that AveXis submit and FDA review one or more BLA supplements, and may take at least several months. However, based on the information currently available, the current product label provides adequate instructions for use of Zolgensma.

Since the FDA reviews of the original BLA are posted on the FDA website, the public has access to some reviews that appear to be partially based on unreliable information.

Of note, based on the AveXis investigation report, AveXis appears to have become aware of the data manipulation as early as March 14, 2019, more than two months prior to the BLA approval; however, AveXis did not inform FDA of the issue until over a month after the BLA approval. If AveXis had informed FDA of this issue prior to the BLA approval, I believe that the approval would have been delayed beyond the PDUFA goal date of May 31, 2019. The delay would have been necessary in order for the FDA to investigate the data manipulation, determine the impact of the data manipulation on the CMC, pharmacology/toxicology, and clinical trial results, and revise the relevant BLA reviews. However, I believe that CBER would have ultimately approved the BLA, based on all information currently available, including compelling evidence of effectiveness and a favorable benefit-risk profile.

Recommendations

1. Zolgensma should remain on the market with the current label (instructions for use), pending the results of FDA further investigation into the data manipulation.

2. FDA should conduct an inspection of AveXis testing site(s) to gather additional data on the nature and extent of the data manipulation.

3. The BLA review team and AveXis should have further discussions to determine the extent to which the original BLA reviews are based on, and impacted by, the manipulated data, and to gather the data necessary to provide reliable, updated reviews of the BLA.

4. Zolgensma lot release should continue to consider the results of the SOP-346 and SOP-347 potency assays, pending further investigation.

5. CBER should make a public statement to inform the public that some of the reviews currently posted on the FDA website are based on data that were manipulated by AveXis, such that those FDA reviews may contain information that is not reliable. To mitigate the likely resulting concern of families and healthcare providers, such a public statement should note that, based on the available information, FDA is confident that Zolgensma, as currently marketed, is safe and effective for the indicated population.