

**From:** [Jarvis, Candace](#)  
**To:** [James L'Italien, PhD \(jlitalien@avexis.com\)](#)  
**Cc:** [Nancy Boman](#); [Byrnes, Andrew](#); [Singer, Mike](#); [Xu, Lei \(CBER\)](#); [Jarvis, Candace](#)  
**Subject:** BLA 125694/0| AveXis, Inc| Information Request 33 (PLEASE RESPOND BY FEBRUARY 8, 2019)  
**Date:** Wednesday, February 06, 2019 9:35:52 AM  
**Attachments:** [image013.png](#) **Importance:** High

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Good morning Dr. L'Italien,

We have the following request for information regarding BLA 125694/0 and request that you respond to this request by February 8, 2019. If you are unable to meet this deadline, please let us know as soon as possible.

1. The submitted draft package insert states that "a maximum weight dosage for a 13.5 kg pediatric patient corresponds to a median weight for a 36-month old SMA Type 1 child based on weight observed in the Pediatric Neuromuscular Clinical Research (PNCR) SMA natural history cohort."
  - a. Please clarify the specific data used to obtain this information; that data was not apparent in the Finkel et al. reference cited, nor in the supplementary figures for that reference available at the Neurology journal web site.
  - b. Please explain why the median weight (rather than some other point of reference, e.g., ninetieth percentile) for a 36-month-old child with SMA type 1 was chosen as the maximum weight dosage.
2. Please provide additional clarification regarding the reasons for using a flat dosage of (b) (4) [REDACTED] /patient for patients weighing more than 13.5 kg.
  - a. You state that "the number of neurons in infants at about 36 months of age is thought to equal the number in adults, hence no need for further linear vg/kg dosing as neuronal mass has been achieved." In the Larsen et al. reference cited, however, the authors note: "We found the newborn brain to contain a neocortical neuron number equal to the adult brain but with a total glial cell number substantially lower than in the adult. The huge growth in brain size in the first years of life is primarily caused by increase in dendritic size together with a fourfold increase in glial cell numbers."
  - b. You further state that "limiting the maximum dose at (b) (4) [REDACTED] /patient provides an acceptable risk/benefit balance because benefit to viable motor neurons is maintained, while the uncertainty of exposing pediatric patients to larger total vector loads based on body weight is also being considered." Please provide the data from your preclinical/clinical studies indicating

greater risk to patients from exposure to larger total vector loads of your product.

Please confirm receipt of this email.

*Regards,*

***Candace N. Jarvis***

*Regulatory Project Manager*

*Center for Biologics Evaluation and Research*

**Office of Tissues and Advanced Therapies**

**U.S. Food and Drug Administration**

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