Inadequate Evidence for Accelerated Approval for BLA# 125781/00 (SRP-9001; delandistrogene moxeparvovec) for the Treatment of Duchenne Muscular Dystrophy

Testimony before the Food and Drug Administration's Cellular, Tissue and Gene Therapies Advisory Committee

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May 12, 2023

I'm Michael Abrams from Public Citizen's Health Research Group. I have no financial conflicts of interest on this matter.

The analysis conducted by Food and Drug Administration (FDA) scientists shows that SRP-9001 (hereafter: 9001) has yet to demonstrate sufficient data warranting its approval to treat Duchenne Muscular Dystrophy (DMD).

The most credible evidence provided by the sponsor for this application comes from the single randomized clinical trial in which 20 subjects received a novel micro-dystrophin gene using a viral-vector and 21 subjects receive placebo.[1] Forty-eight weeks after infusion of 9001, motor functioning was assessed.[2]

Basic analyses did not show significant motor function changes in patients receiving 9001 compared to controls.[3]

Accordingly, the sponsor seeks accelerated approval based on a surrogate marker rather than the usual standard of demonstrated clinical impact.[4] A surrogate endpoint, must per the Accelerated Approval statute be one where there is a scientific consensus that it is "reasonably likely" to yield clinical benefit.[5]

[1] Food and Drug Administration. FDA Briefing Document for BLA# 125781/00. Drug name: delandistrogene moxeparvovec. Applicant: Sarepta Therapeutics, Inc. Cellular, Tissue and Gene Therapies Advisory Committee Meeting. May 12, 2023. https://www.fda.gov/media/168021/download. Accessed May 10, 2023.
[2] *Ibid*. PDF P. 21, 22.
[3] *Ibid.* PDF P. 23.
[4] *Ibid*. PDF P. 6.
[5] Subpart H – Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses. Code of Federal Regulations, Title 21, Volume 5, Section 314.500.

Unfortunately, available clinical and animal data is far from conclusive in that regard.[6] That is likely because micro-dystrophin is an engineered molecule that contains less than half of the structure of natural dystrophin, excluding many plausibly important functional components.[7]

The lone randomized trial (n=40) failed to show that micro-dystrophin protein levels at week 12 correlated with muscle function,[8] a null result that weakens the "reasonably likely" argument for clinical benefit related to this surrogate marker. Instead, such a correlation became evident only when an additional 40 open-label (and thus biased) subjects were added to the analysis.[9]

It should finally be noted that though this DMD therapy is somewhat novel, it has substantial mechanistic overlap (via shortening dystrophin) with four previous accelerated approvals still unconfirmed by FDA-mandated follow-up studies.[10]

Accordingly, it is concerning that a fifth therapy might be introduced based on biochemical mechanisms so tightly aligned with four questionable therapies already on-the-market. Such serial-approvals contradict the concept that speculative, fast-track pathways should be reserved for therapies that "provide meaningful therapeutic benefit…over existing treatments," and where there is a scientific consensus that the surrogate maker is a clear harbinger for clinical benefit.[11]

That is not the case here. Thus, we strongly urge this advisory committee and the FDA to reject application SRP-9001 for accelerated approval.[12] Both effectiveness and regulatory history concerns, not to mention safety, make that rejection necessary.

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[6] Food and Drug Administration. FDA Briefing Document for BLA# 125781/00. Drug name: delandistrogene moxeparvovec. Applicant: Sarepta Therapeutics, Inc. Cellular, Tissue and Gene Therapies Advisory Committee Meeting. May 12, 2023. https://www.fda.gov/media/168021/download. Accessed May 10, 2023.PDF p. 6.
[7] *Ibid.* PDF p. 14, 15.
[8] *Ibid*. PDF p. 33.
[9] *Ibid*. PDF p. 34.
[10] *Ibid*. PDF p. 8.
[11] Subpart H – Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses. Code of Federal Regulations, Title 21, Volume 5, Section 314.500.
[12] Food and Drug Administration. 74th Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) Meeting. May 12, 2023. Discussion Topics and Voting Question. https://www.fda.gov/media/168023/download. Accessed May 10, 2023.