

# An Ethical Case Study Concerning a Patient with Spinal Muscular Atrophy Enrolling in an Expanded Access Program

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## Abstract

We report the case of a 28-year old man with Spinal Muscular Atrophy (SMA) Type II (0 copies of *SMN1* and 3 copies of *SMN2*). He reports worsening symptoms of weakness and muscle fatigue associated with his SMA diagnosis making him a candidate for a compassionate use drug program for Risdiplam run by Genentech. Risdiplam is an SMN modifying agent currently undergoing FDA review for treatment of SMA. Risdiplam would be the first orally administered SMA disease modifying agent if approved. The patient was accepted to be screened for this program. Prior to his screening visit, he experienced an acute medical problem which could potentially disqualify him. We will discuss the ethical issues regarding his participation in the program.

## Background

- 5q-related spinal muscular atrophy (SMA) is an autosomal recessive disorder that occurs in about 1 in 11,000 births and results in degeneration of motor neurons causing progressive muscle weakness.<sup>3</sup>
- Homozygous deletions or pathogenic mutations in the survival motor neuron 1 gene (*SMN1*) lead to deficiency in SMN protein. The carrier frequency is approximately 1 in 40 to 1 in 67.<sup>3</sup>
- Disease severity is based on the copy number of *SMN2*, a paralogous gene. *SMN2* contains an amino acid substitution at a key exonic splicing enhancer site resulting in a nonfunctional and truncated protein that is rapidly degraded. Only a small fraction of *SMN2* transcripts encode full-length SMN protein.<sup>3</sup>
- There are currently 2 FDA-approved disease modifying treatments for SMA on the market: Nusinersen (Spinraza) and Onasemnogene abeparvovec-xioi (Zolgensma).<sup>1</sup>

Drug	Type	Target	Route	Cons
Nusinersen (Spinraza)	Antisense oligo-nucleotide	Exon 7	Intrathecal	Hard to administer to patients with a spinal fusion and/or severe scoliosis
Onasemnogene abeparvovec-xioi (Zolgensma)	Gene therapy	Exon 7	Intravenous infusion	Restricted to patients under 2 years old
Risdiplam	Antisense oligo-nucleotide	Exon 7	Oral	Not FDA approved

## Case Description

- The patient is a 28-year-old man who was formally diagnosed with SMA Type II at age 1.5 years. He was never able to walk.
- SMA genetic testing through Invitae revealed homozygous deletion in *SMN1*. His *SMN2* copy number is 3.
- He reports worsening muscle weakness and fatigue which affects his ability to eat and perform his activities of daily living.
- He has restrictive lung disease due to severe scoliosis and diaphragmatic weakness. He is on non-invasive ventilation at night. His past medical history is significant for a spinal fusion.
- We do not have the ability to dose Nusinersen at UCH due to his complex spinal anatomy.**
- Patient was accepted for screening for the Risdiplam Expanded Access Program (EAP).
- Before screening for the EAP, he developed acute vision changes including blurry vision and was seen in a local ER. **He was noted to have elevated intraocular pressures and was diagnosed with acute open-angle glaucoma of both eyes.**
- Data from animal studies showed an increased risk of developing/exacerbating ophthalmologic diseases with Risdiplam use.
- The initial EAP version listed a recent history (less than a year) of ophthalmologic disease as an exclusion criteria. A later version of the protocol removed this component, however. Of the **245 clinical trial patients** monitored before the protocol change, **none presented with signs of retinal toxicity.**
- After leaving the hospital, the patient was re-evaluated by a local ophthalmologist who thought his acute glaucoma was a result of steroids in his Flonase nasal spray. He was given Latanoprost drops for his symptoms. His symptoms rapidly improved and he was able to stop the drops.
- Subsequent ophthalmological evaluation noted normal pressures and no signs of current ophthalmological disease.**
- What would you do in this clinical scenario?

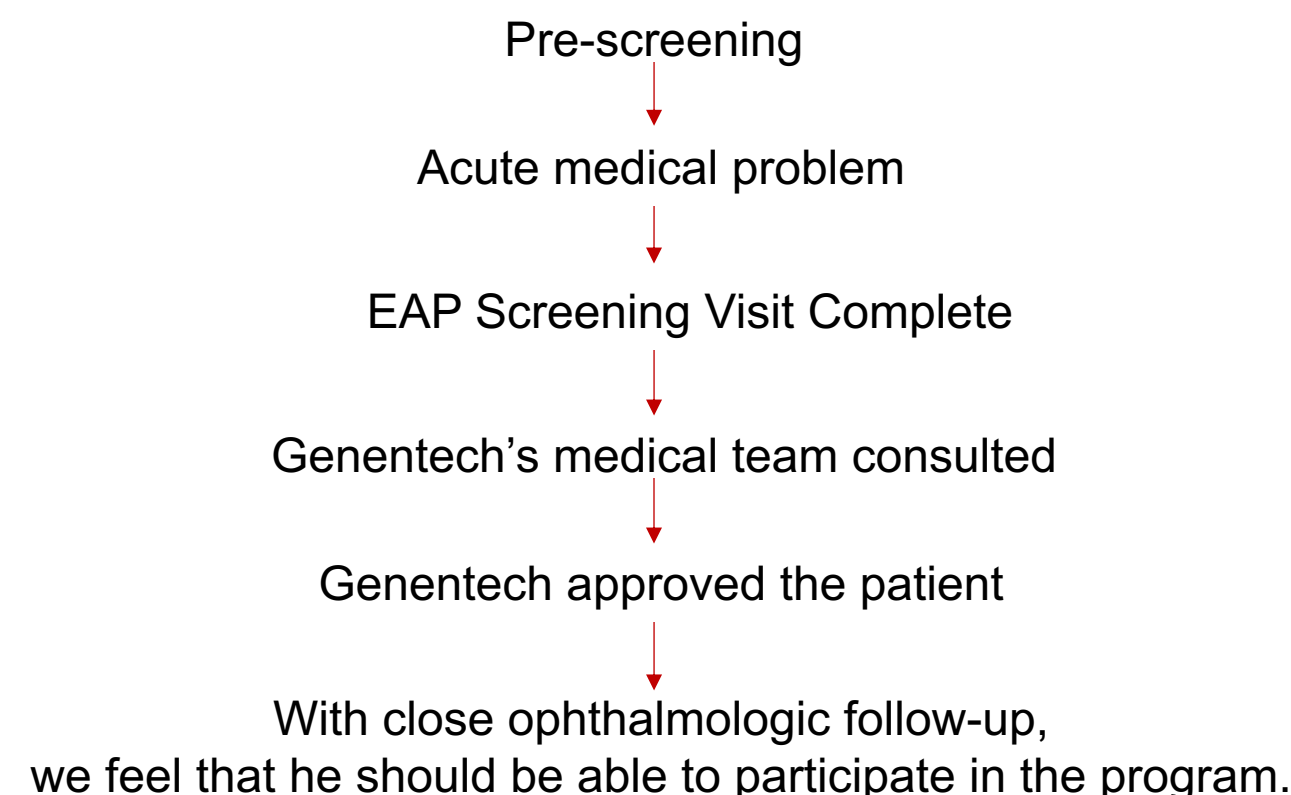


Figure 1. Case Study Timeline

## Discussion

In animal studies of Risdiplam, retinal toxicity was reported; however, in human trials, there were no incidences of retinal toxicity reported.

### Ethical considerations:

- Knowing there may be increased ophthalmological risk, would it be safe to administer Risdiplam to this patient?
  - When Nusinersen was released to the market, a major concern about the drug was whether the potential harms were being underestimated.
  - With Nusinersen, there was not enough long-term follow-up on the 200 patients enrolled to determine whether the disease progression slowing continues with longer-term treatment, whether there were significant effects for patients with different severity of disease, and whether there were longer term side effects.<sup>2</sup>
    - Patients on Risdiplam were only followed for 1-2 years with ophthalmological evaluations and patients were not assessed in the setting of acute ophthalmological issues.
- If an adverse event occurred in this patient, how would this affect FDA approval of the drug?
  - All side effects will still be reported and could change the the FDA review process and possibly delay the FDA's decision regarding the drug.
    - Approval for Risdiplam could be delayed if an adverse event occurred, thus delaying treatment for many other SMA patients.

## Ethical Considerations

- Verbal consent was obtained by the patient for this poster.
- Written consent was obtained for the patient's enrollment in the EAP.
- During the consent process, the PI and patient extensively discussed ocular concerns and his unique potential risk.

## Acknowledgements

- DREAM program at the University of Colorado School of Medicine
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## References

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