Attachment—Additional Questions for the Record

Subcommittee on Health
Hearing on
"The Path Forward: Advancing Treatments and Cures for Neurodegenerative Diseases"
July 29, 2021

Jinsy Andrews, M.D., Director of Neuromuscular Clinical Trials, Columbia University, The Neurological Institute

The Honorable Nanette Diaz Barragán (D-CA)

1. Can you identify any drugs that would have met the FDA's "substantial evidence" test for drug approval if they had only been tested against a trial endpoint of one domain on the ALSFRS-R scale instead of against all 4 domains?

2. If a patient arrived at your office with early symptom onset – and you had not conducted an EMG – could you testify to a "reasonable degree of medical certainty" about their ALS diagnosis based only upon the criteria in the ALSFRS-R domains?

3. Can you explain how the ROADS test developed at Emory University differs from the ALSFRS-R tool? How long will it take before that tool could be validated & implemented as a measure for the primary endpoint in ALS trials?

4. In an MGH press release, you described the Brainstorm NurOwn ALS biomarkers as "robust." If those biomarkers are correlated with responders in the Phase 3 trial, under the current regulatory structure, how many studies would it take or how many years would you estimate would pass before those biomarkers could be "validated" & used as a surrogate endpoint for efficacy in an ALS trial &/or to eliminate the need for placebos in ALS trials?

5. It is our understanding that ANSWER ALS is conducting an OMICS study on 1000 people with ALS & through its use of iPSC cells, it is innovating research in a personalized medicine approach to ALS that may help address the issues related to heterogeneity in the disease. Given the heterogeneity in ALS, if the NIH were to fund an OMICS study for ALS, what would forecast the optimal number of patients for such a study & the cost per patient?

6. What do you believe the top 5 most promising biomarkers are for ALS?

7. Can you describe how COVID impacted clinical trials you are/were conducting in ALS?

8. Your colleague, Dr. Shneider at Columbia, is renowned as one of the top specialists in juvenile forms of ALS. He led research into a mutation called FUS that impacted twin sisters from Iowa. That NIH funded research has resulted in a drug being developed & now tested in clinical trials for both juveniles & adults with ALS.

   A 5-year-old boy named "KN" was recently diagnosed with ALS. He has a mutation in SPTLC2. With NIH funding, will Columbia commit to helping research the SPTLC1 & SPTLC2 gene affecting juveniles of African descent?

9. As you are aware, lack of access to health care is an issue in underserved communities. Can you explain how this same lack of access to health care impacts the delay in diagnosis and eventual qualifications for clinical trials?

10. ALS Centers of Excellence such as MGH, UMass, Columbia, MAYO, likely have a much higher percentage of their patient population enrolled in clinical trials than smaller clinics in less populated states. Do Mass General or Columbia collect data on what the distribution of patients is across the states, and can the FDA provide that data so that we may assess the availability of access to clinical trials to people in underserved communities?

11. Can the ALS Association work with an HBCU to establish an ALS Center of Excellence at one of those institutions?

12. Can you opine if there are features of another country's regulatory structures that would help expedite drug approval for ALS without jeopardizing safety?

13. Before this Committee's hearing in 2015, former Commissioner Gottlieb testified that "adverse events" in EAPs had never impacted drug approval. FDA officials authored 2 studies validating his statement and then FDA training called that a "myth" perpetuated by drug sponsors. Are you aware of any updates to that research in the last 5 years?

14. Can you describe the hurdles that small pharmaceutical companies have expressed to you, preventing them from offering Expanded Access to more people with ALS who don't qualify for trials?

15. Can you describe the different hurdles for EAPs or OLEs for a drug overseen by CDER versus a personalized biologic overseen by CBER? Is there anything Congress can do from a regulatory perspective to maximize or encourage drug sponsors to offer EAPs or OLEs?

16. In your career:

    a. In how many ALS trials have you been a principal investigator?

    b. How many peer-reviewed studies have you authored for ALS?

c. How many ALS patients do you estimate you have seen?

17. Can you estimate how many times in your career have you had to deliver the bad news to a patient that they have ALS?

18. In a study published a few months ago, the authors found significant differences in the expression of genes in men with ALS vs women with ALS. Can you please explain that study and how that gender and epigenetic heterogeneity could impact a drug's efficacy proof?

19. Columbia is a leader in genetic research in ALS. Can you explain how many samples you have in your database and what a population wide genome study would do to further ALS drug development and personalized approaches to treatment?

20. Would you recommend Congress pass regulations to ensure genetic testing is the standard of care in not only ALS but other rare, imminently life-threatening diseases with no disease modifying treatments?

21. Although representatives of the CDC are not present today, would it be your recommendation to make ALS a mandatorily reported disease at the federal level just as you have done in Massachusetts?

22. What percentage of ALS cases have limb onset?

    a. What percentage are upper limb versus lower limb onset?

    b. What is the percentage that have asymmetric onset?

23. In the 21st Century Cures Act, Congress encouraged the use of "Real World" Evidence to avoid the need for placebos in trials. It is my understanding that there is a database called PRO-ACT that contains data from 10,000 patients in placebo-controlled ALS trials. Can you help us understand why that database is not sufficient to eliminate placebo-controlled trials in ALS?

24. Acting Commissioner Woodcock, has frequently spoken about how the "War on Cancer" & its concurrent increase in funding resulted in expedited research & treatments. She has suggested that neurodegenerative diseases need a similar "War." What percentage of ALS research applications receive grant funding? If you were the decision maker for a War on ALS, what amount of annual funding do you believe it would take?

25. Are you aware of how the suicide rate in ALS compares to the national suicide rate or the suicide rate for oncological diseases?

26. Based on feedback from my constituents, it appears many are desperate to qualify for clinical trials. Are you aware of or would it surprise you if people with ALS delayed going onto ventilation until after they qualified for a clinical trial? What effect would that delay likely have on the ALSFRS-R score both before & after receiving breathing

assistance once a trial began? Same question for a delay in getting a feeding tube in order to qualify for a trial?

27. Can you explain the paradigm of why drug sponsors have strict trial exclusions in ALS and patients who are my constituents want broader inclusion criteria? How does broader inclusion criteria risk trial outcomes for efficacy in ALS? Have you ever had broader inclusions criteria jeopardize trial outcomes?

28. Do you remember the movie, "Dallas Buyers Club" with Matthew McConaughey? In that movie, people with HIV were buying unapproved drugs from other countries. Are you aware of a similar Dallas Buyers Club in ALS? Do you believe the slow FDA approval process is:

    a. forcing Americans to try drugs off the black market?

    b. having a compounding pharmacy attempt to duplicate a drug in trials as happened with Neuraltus' NP001?

    c. or traveling to foreign countries for specious stem cell therapies?

    Would you rather that your patients received a therapy in a rigorously controlled Phase 4 study instead of a black-market unapproved drug aka - Dallas Buyers Club mentality?

29. If you could recommend to Congress three regulatory changes that would expedite drug development & approval in ALS, what would those changes be?

Thank you very much for your interest in finding treatments and cures for people living with ALS and the invitation to respond to your 29 questions.

Unfortunately, my responsibilities as Director of Neuromuscular Clinical Trials at Columbia University do not allow me the time to respond.

I have asked staff at the ALS Association to follow up with your staff on Act for ALS and other legislation of interest.

Jinsy A. Andrews, MD, MSc
Columbia University Irving Medical Center