Testimony Before the FDA's Peripheral and Central Nervous System Drugs Advisory Committee: A Lack of Substantial Evidence of Effectiveness for NDA# 216660, AMX0035/Sodium Phenylbutyrate and Taurursodiol, for Treatment of Amyotrophic Lateral Sclerosis

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(I have no financial conflicts of interests)

FDA identified too many concerns and limitations regarding the phase 2 CENTAUR trial and its open-label extension

1. Small study, short duration
2. Randomization-implementation problems
3. Modest p-values, modest effect sizes
4. Non-significant secondary outcome effects
5. Methods that ignored loss of data due to patient deaths
6. Enrollment/disenrollment problems and imbalances
7. Questionable linearity assumption of the functional scales with time
8. Unblinding concerns
9. “Not persuasive,” and “not interpretable” open-label follow-up study

FDA's penultimate briefing statement…

"The FDA draft guidance on substantial evidence states: 'Reliance on a single, large, multicenter trial to establish effectiveness should generally be limited to situations in which the trial has demonstrated a clinically meaningful and statistically very persuasive effect on mortality.'"

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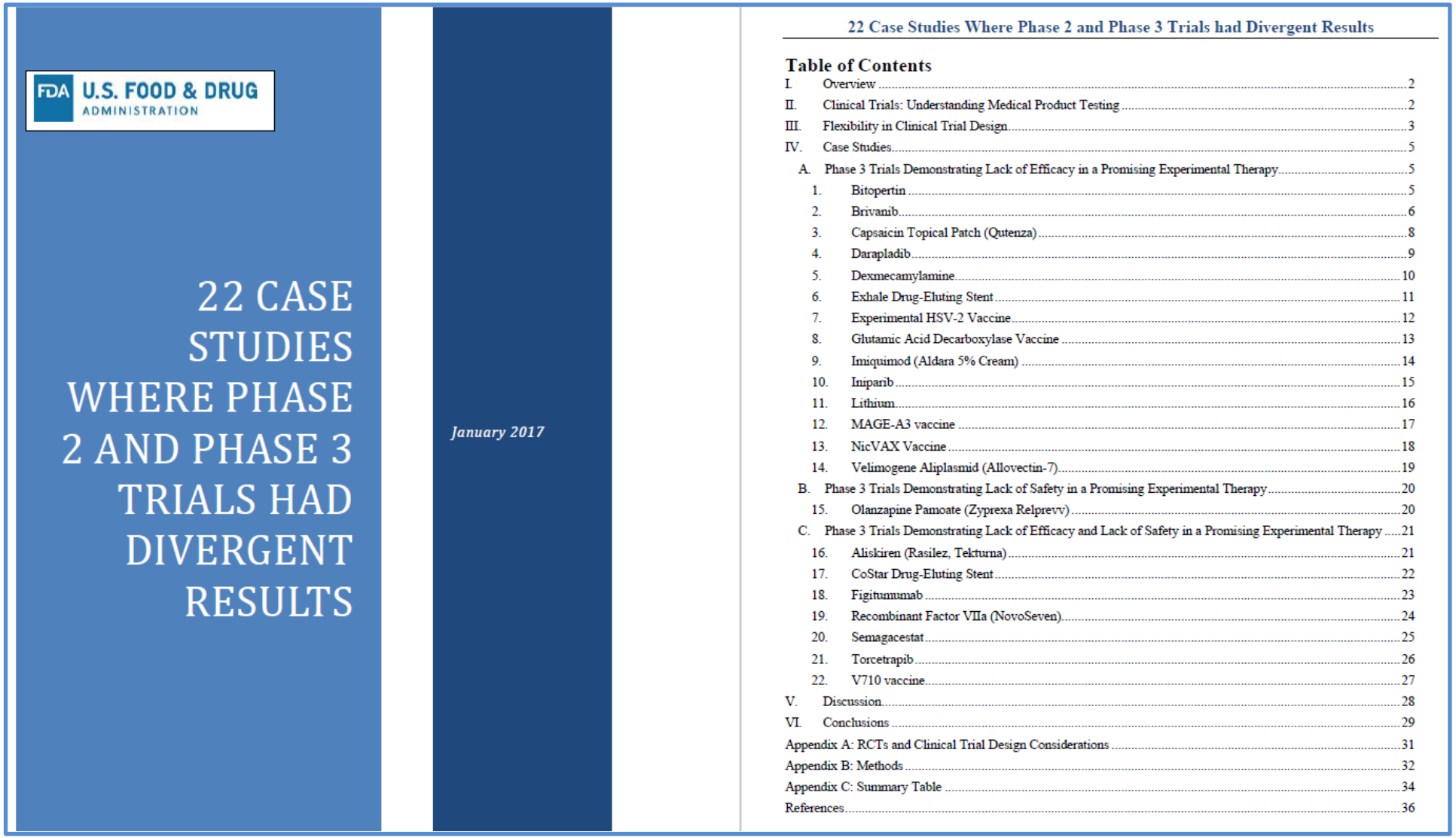
Phase 2 ≠ Phase 3



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22 CASE STUDIES WHERE PHASE 2 AND PHASE 3 TRIALS HAD DIVERGENT RESULTS

January 2017

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Conclusions

- There is presently lack of substantial evidence that AMX0035 is effective for the treatment of ALS, and the FDA should await the results of the ongoing phase 3 trial before giving the drug further consideration.

- We therefore urge the committee to vote “No” on the question: Do the data from the single randomized, controlled trial and the open-label extension study support a conclusion that sodium phenylbutyrate/taurursodiol is effective in the treatment of patients with ALS?

- We finally observe that though the “FDA has long stressed the appropriateness of exercising regulatory flexibility…for serious disease with unmet medical need,” it must do so “while preserving appropriate assurance of safety and effectiveness.” In this case, such flexibility is unacceptable.