Testimony
of

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1. Chairman Paul, Ranking Member Casey and Distinguished Members of the Subcommittee, my name is Dr Michael Strupp, a Professor of Neurology at the University of Munich, Germany in the Department of Neurology and German Centre for Vertigo and Balance Disorders.

2. Thank you for the opportunity to discuss the current status of orphan drug development, and how the process of getting new treatments to patients with rare, fatal, genetic conditions can be improved so that patients have access to potentially life-changing treatments sooner, and the extremely high medical need of too many orphan disorders can be met.

3. My clinical expertise is concentrated on diagnosis and therapy for vestibular, ocular motor, and cerebellar disorders, namely by discovering, investigating, and the "repurposing" of drugs by initiating, designing, and performing randomized controlled clinical trials (mainly investigator initiated) that include multinational studies. This also involves performing back-translational research in animal models.

4. Some of my major achievements in discovering and assessing new treatments have been: First, demonstration of the effectiveness of vestibular exercises in acute vestibular neuritis in a controlled clinical trial. Second, demonstration of the benefit of steroids in acute vestibular neuritis, a placebo-controlled, four-arm trial published in the New England Journal of Medicine. Third, introduction of three new pharmacotherapeutic principles for the treatment of rare diseases: (1) aminopyridines, as potassium channel blockers, for the

treatment of downbeat, upbeat and central positioning nystagmus as well as episodic ataxia type 2 (now the treatment of choice for episodic ataxia type 2 according to the American Academy of Neurology, 2018); (2) chlorzoxazone for the therapy of downbeat nystagmus; and, more recently, (3) N-acetyl-leucine for the treatment of ataxias (such as inherited cerebellar ataxias like Ataxia-Telangiectasia and Spinocerebellar Ataxias), Niemann-Pick Type C (NPC), Tay-Sachs disease, as well as additional rare lysosomal storage disorders and neurodegenerative diseases.

5. I have been the principal investigator of the following randomized controlled trials on: episodic ataxia type 2 (in collaboration with Dr Joanna Jen, UCLA), downbeat nystagmus (in collaboration with Dr Christopher Kennard, Oxford), Menière's disease, vestibular neuritis, vestibular migraine, vestibular paroxysmia, benign paroxysmal positional vertigo and ataxias.

6. Since 2016, I have been the head of the task force for the pharmacotherapy of cerebellar disorders.

7. I have also extensive experience in managing patients with rare, neurodegenerative diseases, in particular, cerebellar ataxias, NPC (including the 2017 "Recommendations for the detection and diagnosis of NPC" with Dr Marc Patterson, Mayo Clinic) and Tay-Sachs disease. I have also carried out both experimental researches to identify potential therapies for these patients. The background for this basic and clinical research has been an international collaboration requiring colleagues and experts' involvement from around the world. Back-translational research has also been done in various animal models, e.g., in close collaboration with Professor of Pharmacology and Neurology from various global institutions.

8. I have authored 366 PubMed listed papers and four books on vertigo, dizziness, ocular motor and cerebellar disorders. Currently I am the Editor-in-Chief of Frontiers in Neuro-otology, Joint Chief Editor of The Journal of Neurology, and a Member of the Editorial Board of Neurology. I have received many clinical and scientific awards, including the Hallpike-Nylen Award 2106, am a very engaged teacher and was awarded 'Best Teacher' by the German Neurological Society.

9. Finally, I am a very passionate doctor, and personally see more than 2000 patients per year, and am a proud father of four kids.

10. My curriculum vitae is attached.

Problem Statement

11. The responsibility of any clinician is to provide their patients with the best standard of care to manage their underlying conditions. Diagnosis is the traditional basis for decision-making in clinical practice and can provide crucial information on treatment options that influence outcome. Clinical management of rare, genetic, orphan diseases—a majority of which are progressive, debilitating, and display a large degree of clinical heterogeneity— follows a similar clinical practice paradigm to precisely diagnose the disorder, for instance, by genetic testing. In other words, delivering the best standard of care ideally requires clinicians do not simply treat symptoms of unknown etiology but identify the disease with a known underlying pathophysiological mechanism to apply a specific individualized therapy.

12. In my professional experience spanning 20 years as a neurologist, I have continuously diagnosed and treated patients with various different rare, genetic diseases. Such diseases often manifest in early childhood and are often associated with a decreased life-expectancy. Almost all of these diseases are associated with a severe impairment of functioning and quality of life. There is therefore a need to recognize the significant disease burdens on both the patient as well as their families and caregivers.

13. For a majority of rare diseases, there are currently very few, if any, effective treatment options. For over 95% of orphan diseases, there is no US Food and Drug Administration (FDA) approved treatment medically available to help treat their condition. [1]

14. As part of my clinical practice, I have been fully committed throughout my career to identifying novel pharmacotherapeutics which could positively impact the quality of life of my patients and improve their standard of care. Throughout my research efforts, I have discovered three new potential therapeutic options (use of aminopyridines, Acetyl-Leucine

[1] https://globalgenes.org/rare-diseases-facts-statistics/

and chlorzoxazone) for the treatment of rare diseases based on a therapeutic rationale to justify further clinical development. Specifically: the pharmacological agent should be approved for other indications so that it can be "repurposed" for therapeutic use in a rare disease setting; there should be available evidence in other disease settings to establish an acceptable safety profile in humans; there should be sound scientific evidence from animal studies elucidating the compounds mode of action and specific effects in particular diseases to establish the therapeutic potential of the re-purposed agent to treat a rare disease.

15. In my 20 years' experience in treating rare, often fatal, genetic disease, I have become acutely aware of the barriers which often limit potentially life-changing treatments from becoming available for rare disease patient communities. My personal perspective has also been shaped by my own experience as the initiator and principal investigator of seven "investigator initiated trials" (IITs), as well as my interactions and relationships with my rare disease patients and their families.

16. These experiences and interactions have helped me to identify specific considerations that are of practical relevance to research and development of new treatments for orphan diseases. From this basis, I believe the following issues ought to be considered and resolved in order to facilitate research and development of new treatments for orphan diseases.

New "Gold Standard" for Rare Disease Trial Design

17. In a progressive, life-threatening condition, there is a greater immediacy for trials to be carried out and in a maximally efficient manner so that the new treatment can be made available before the possible window of therapeutic opportunity is lost. There is an urgency from patients with rare, fatal diseases to have access to potentially life-changing treatments before they are too far progressed, or pass-away due to an absence of therapies.

18. Patients with rare, fatal diseases would benefit if regulatory authorities could collaborate more closely to design non-clinical programs, clinical trials, and endpoint assessments that are relevant to what is known both about the product-specific nature of the active pharmacological substance, and the patient population it intends to treat.

19. For example, non-clinical safety pharmacology studies in animals that assess the reproductive and developmental toxicity, carcinogenicity, and fertility and early embryonic development for diseases that predominately affect pediatric patients and are highly debilitating, rapidly progressive, and fatal, could be agreed to be conducted post-approval, or waived in exceptional circumstances on a case-by-case basis taking account of the severity of the disease and the patient characteristics.

20. The current conventional "gold standard" for a randomized, controlled trial (RCT) that shows statistical significance of $p < 0.05$ is often not an appropriate approach for a trial designed for rare, fatal, orphan diseases that progress rapidly and have high clinical heterogeneity. While RCT are desirable to establish clinical efficacy against a very high regulatory standard, their practical implementation can be challenging in a rare disease setting. Moreover, there are important medical and ethical concerns about certain RCT against a placebo to establish the therapeutic effects of the new treatment that may inhibit the rate of patient enrollment.

21. Parents and caregivers often have legitimate ethical concerns about placebo-controlled trials. This makes recruitment a long, difficult and complicated process, delaying the time it takes to get treatments to patients. It also greatly increases the costs of studies as multinational centers are needed to recruit a likely even smaller pool of willing patients.

22. This risk is even greater for trials involving drugs that are already approved for use in another clinical setting, i.e. "repurposed drugs" and could be readily accessed by patients for use in an off-label/unlicensed setting. In such circumstances, patients or their families may be reluctant to participate in a placebo-controlled study where there is a 50% chance that the trial participants receive an inactive treatment.

23. The standard approach to statistical significance is a prerequisite for large trials in diseases with a high incidence or prevalence, but for orphan populations this is hard to achieve in view of the rarity of occurrence of the disease and limited number of patients who are eligible for enrollment.

24. Many rare diseases are at a dual disadvantage due to the small sample sizes and the combination of high inter-individual variability in clinical course of the disease. This significantly diminishes a study's statistical power to detect a therapeutic effect.

25. In too many instances, when a compound fails, it is not clear if this is due to a lack of a biological effect rather than a failure due to an inadequate study design that was not compatible with what can be reasonably asked of, and measured within the rare disease patient population. Early collaboration with the regulators allows for alternative trial designs, in particular clinically relevant end-points, and statistical techniques that maximize data from a small and heterozygous patient population and increase ability to demonstrate effects of a treatment.

26. In rare diseases, a more balanced approach using smaller sample sizes and a wider array of assessments may be justified to establish the true clinical effects and patient-oriented benefits of the new treatment.

27. Clinical programs should be designed to consider the realities of the demographics of the patient population and their unique medical need should be the "gold standard" for developing orphan drugs so that they get to patients sooner.

Assessing Clinical Meaningful Effects

28. To get treatments more speedily to patients, the therapeutic effects should be established by reference to a wider range of data, including animal models, compassionate use data and patient/family self-reporting should be used to assess the efficacy and risk-benefit of a treatment. Such a holistic approach to evidence generation will serve our patients better, particularly in view of a clear unmet need for new treatments, and provide our patients with the optimal care that treating physicians strive to achieve as the clinical objective.

29. In orphan diseases that are rapidly progressive and display a wide range of debilitating symptoms, the best measurement clinicians have to determine whether a treatment improves patients' functioning and quality of life is to actually listen to the voices of patients and their families/caregivers' voices.

30. In patient populations with a huge variability of clinical symptoms, medications often produce different benefits in different patients, and it is not responsible to select a single measurement that is described as "clinically meaningful" for every patient success of the trial hinges upon.

31. In addition, quantifiable endpoints like biomarkers or symptom-rating scales may in fact be irrelevant for a patient's quality of life, level of functioning, or capabilities.

32. Therefore, in orphan disease trials, a wider use of clinical outcomes, including clinical impressions from neurologists experienced in treating rare conditions and familiar with the patient's individual disease presentation, as well as patient/family/caregiver reported outcomes should be the standard of success, and prioritized over statistical significance on a single primary endpoint.

Conditional Approvals and Continued Safety Monitoring:

33. A greater use of conditional approvals should be applied by the regulatory authorities to get drugs sooner to patients with high unmet medical needs. If an acceptable risk-benefit profile of the drug is established, albeit based on a dataset that is less than perfect, in the circumstances of treating rare, fatal, rapidly progressive diseases, it should be made available for clinicians to treat their patients in a controlled setting without delay.

34. In cases of fatal conditions and small patient populations which makes trials more difficult, post-approval rolling monitoring of safety and efficacy in patient populations is preferable as it provides direct evidence on whether the drug is used safely and effectively in a real-world clinical practice. Such evidence is far more relevant than data generated in an artificially designed clinical trial setting.

35. Similarly, individual, personalized assessment could be a more feasible way to assess the treatment effect in ultra-small patient populations. In this scenario, the expert clinician assess the patient's condition while on medication for a defined treatment period, as well as their condition after stopping the medication, to determine the individual's response and if the medication can be continued. This approach is contingent on the safety and tolerability

of the drug, but allows patients with unmet medical needs access to potentially life-changing treatments faster.

36. Conditional approvals and individual assessments could be excellent ways to meet the extremely high unmet medical need of far too many rare diseases. These are also often preferable to long development programs because many of these rare conditions are fatal in the early phase of childhood and children do not survive to adulthood. As clinical presentation evolves, these young and small populations will face difficulties transitioning from pediatric to adolescent while waiting for new treatments, and often regress too much or die before effective treatments are available.

37. Use of conditional approvals, based on the considerations of the unique risk-benefit profile an orphan drug has for its target patient population, and even, an individual patient, will get treatments to patients who simply cannot wait for perfect study data to be generated in pursuit of a specific scientific endeavor.

38. In summary, the non-clinical and clinical development programs for rare diseases should be realistic and implementable so that the right level (while not perfect according to the "gold" standard commonly applied to new treatments for larger populations) of evidence is generated to make an informed assessment of whether the benefits outweigh the risks. For re-purposed substances, the risks of the pharmacological agents in humans would have been established and such experience is highly relevant in the overall benefit/risk assessment.

Case Studies: Acetyl-Leucine

39. An example of a novel drug I discovered that is a potential treatment for rare, genetic diseases is a modified amino acid ester that is orally delivered: N-Acetyl-Leucine (which can be formulated as the racemic compound N-Acetyl-DL-Leucine, or single enantiomers N-Acetyl-L-Leucine and N-Acetyl-D-Leucine). Based on the available evidence, N-Acetyl-L-Leucine is believed to be the optimal form. Given the high unmet medical need, N-Acetyl-L-Leucine is initially being developed by IntraBio Inc for the treatment of three rare, genetic diseases: Tay-Sachs diseases, NPC, and inherited cerebellar ataxias (such as Ataxia

telangiectasia, spinocerebellar ataxias, and Ataxia with Oculomotor Apraxia) before it is investigated for the treatment of broader neurodegenerative conditions such as Alzheimer's.

40. N-Acetyl-DL-Leucine has been approved in France since 1957 for the treatment of vertigo. The drug has been used in 10s of millions of people and over 100s of millions of dosages, and has a very well-established safety profile.
41. Based on evidence that N-Acetyl-Leucine impacted vestibular symptoms, I hypothesized the compound could have effects on ataxia patients because of the close anatomical, physiological and pathophysiological interaction between the cerebellar and vestibular systems.
42. Due to its established safety profile in vertigo, and what is known about the active pharmaceutical substance, compassionate use studies in Europe began for a limited number of patients with rare lysosomal storage disorders and neurodegenerative diseases. The effects of N-Acetyl-Leucine have now been observed in 18 indications, including Niemann-Pick type C (NPC), Tay-Sachs disease, and inherited cerebellar ataxias, as well as Lewy Body Dementia and Parkinsonian syndromes. In these diseases, the compound has been observed to have an effect on improving various neurological symptoms, including ataxia, coordination, gait and cognition as well as "functioning", and quality of life.
43. Subsequent *in vitro* and *in vivo* animal studies in diseases models such as NPC and Tay-Sachs disease have demonstrated symptomatic and even neuroprotective effects of the compound in both diseases. The dosage per KG in the animal models was equivalent to the dose used in patients, further evidence for its potential safe and effective clinical benefit.
44. In total, the large body of research formed over the past 10 years, produced by myself and fellow neurologists and clinicians, as well as pharmacologists and chemists, is evidence that shows the compound is safe and offers a good risk-benefit profile for these rare, genetic diseases. This is supportive of 60 years of established safety data generated by the compounds approved use in acute vertigo in France.
45. However, despite what is known about the active pharmaceutical substance, and the nature of these rare, fatal, rapidly-progressive diseases with no available treatments, the development of N-Acetyl-Leucine has been almost the same as drugs intended to treat broad, common, non-serious diseases.

46. As an example: the FDA requests a juvenile animal toxicity study (a year-long study) be conducted before N-Acetyl-Leucine is trialed in the US for pediatric patients (although they are over 50% of the patient population). Taking into account what has already been documented in another clinical setting regarding the active pharmaceutical substance, which provides reasonable confidence in the safety based on prior human exposure, this study does not complete the "knowledge gaps" and provide a greater understanding of pharmacological properties, but it does significantly delay clinical trials for patients with high unmet medical need.
47. Similarly, the clinical development of N-Acetyl-Leucine is still contingent upon demonstrating its success in randomized controlled trials with quantifiable data. However, from compassionate use experience, where quantifiable data demonstrating N-Acetyl-Leucine's statistical significance has been generated, we have also observed the significant value of assessing wide range of evidence, including reports from clinicians and families qualifying the compounds effect, to dozens of videos demonstrating the treatment effects. In a randomized controlled trial setting, these clinician and patient reported outcomes are still considered to be secondary and not relevant for regulatory approval, because they cannot be quantified and turned into traditional statistics. This has the potential of demonstrating a false-negative for the efficacy of a compound which could be indeed beneficial.
48. Evidently, the current regulatory requirements for every new proposed drug create barriers for getting potential treatments to patients with huge medical needs. Although it is necessary to properly establish the good risk-benefit profile of any treatment, the longer this process, the higher the potential patients turn to dangerous alternatives, like unlicensed use or using chemical grade products, due to their extremely high unmet medical need.

Actions

49. As a clinician, it is my responsibility that patients receive products whose quality is suitable for clinical use. Especially for conditions that are fatal and debilitating, it is important these products are investigated under the supervision of a clinical expert or specialist to determine their true risk-benefit profile.

50. So that treatments of clinical quality can be made available sooner for clinicians use to care for their patients with rare, fatal diseases, the necessity of demonstrating a good risk-benefit profile needs to be defined within the context of the rare patient population's unique, unmet medical needs. Regulators and orphan drug developers have to exercise a sense of proportion when designing development programs so that the development process is ethical, efficient, and achievable, and patients must always come first with the prerequisite that an agent has been shown to be safe.

51. Most importantly, to improve the lives of patients with rare, fatal, often rapidly progressive, debilitating genetic diseases, we must listen to the voices of patients, their families, and caregivers so that the clinical effects are put into a proper clinical context.

52. There is no better judge to determine if a treatment will improve a patient's functioning and quality of life than the patient, their families, or caregivers, because no one will know better than what life with such diseases entails than patients, their caregivers, and their families—even neurologists like myself (and as a father of four children).