**A Pharmacologic Strategy for Genetic Complementation in X-linked ALD: Novel Use of the Thyromimetic Compound Sobetirome**

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Our long-range goal is to test the potential of sobetirome, an experimental selective thyromimetic drug, as a treatment for X-linked adrenoleukodystrophy (X-ALD), an inherited neurodegenerative disorder with no effective therapy. X-ALD is caused by mutations in the ABCD1 gene, which encodes a peroxisomal membrane transporter (ABCD1) required for very long chain fatty acid (VLCFA) metabolism. The defect in VLCFA metabolism in X-ALD can be corrected by the closely related protein ABCD2, suggesting that manipulation of ABCD2 expression may have therapeutic potential. Both ABCD1 and ABCD2 are transcriptionally regulated by thyroid hormone, leading to the hypothesis that sobetirome may have efficacy as a treatment for X-ALD. Selective thyromimetics such as sobetirome that lack the adverse thyrotoxic effects of thyroid hormone have been shown to be safe and efficacious as lipid-lowering agents. The FDA viewed our hypothesis favorably as evidenced by granting an Orphan Drug Designation for use of sobetirome in X-ALD. We propose a pilot study in which we will administer sobetirome for up to 30 days in a small number of X-ALD patients. The primary outcome measure will be VLCFA levels, which are elevated in X-ALD patients. This study will be the first step in a long-term development program, and if successful, we envision a future grant from the Orphan Products Division of the FDA and the subsequent recruitment of industry partners to fund the continued development and commercialization of sobetirome for X-ALD, based on the novel mechanism of genetic complementation via transcriptional activation of ABCD2.