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**PRESETATION TITLE: How late should a new drug development program be kept in the academic space? Late-stage exemplars of viltolarsen and vamorolone."**

**ABSTRACT**: Viltolarsen (Viltepso) is a precision medicine, exon-skipping drug developed and marketed (USA and Japan) for Duchenne muscular dystrophy (patients amenable to exon 53 skipping; PMO oligonucleotide chemistry). Vamorolone is a first-in-class dissociative partial agonist of the glucocorticoid receptor developed as a safer alternative to corticosteroid standard of care in DMD, currently under FDA NDA and EMA MAA review. The clinical development of both drugs leveraged an established academic clinical trial network (Cooperative International Neuromuscular Research Group; CINRG) and were led by academic international neuromuscular disease experts. Viltolarsen was first developed by Dr. Shini'ichi Takeda of the National Center for Neurology and Psychiatry in Kodaira Japan, and parallel harmonized clinical trials in the US (CINRG) and Japan were carried out with a primary outcome of *de novo* dystrophin production in muscle (accelerated approval pathway). The CINRG academic clinical trial infrastructure was leveraged to both carry out the US trial, as well as providing extensive natural history data for exploratory studies of viltolarsen-related efficacy of motor outcomes (CINRG DNHS). In the US trial, dystrophin rescue was seen at ~6% of normal (wild-type) levels, with exploratory clinical evidence of efficacy vs. CINRG DNHS external compactors over both 6 months (Clemens et al. 2020) and 2 years (Clemens et al. 2022). Vamorolone, a potential alternative to corticosteroid standard of care, was developed by removing a key oxygen moiety from the 11β site of the steroidal ring, making it distinct from the other 33 members of the corticosteroidal drug class. This modification removed the active site of the modulatory HSD11B1 and HSD11B2 enzymes (hydroxysteroid dehydrogenases), reduced gene transcriptional activity, and added potent mineralocorticoid receptor antagonist activity. In a double-blind, placebo- and prednisone-controlled clinical trial of 121 DMD boys, vamorolone showed similar efficacy to corticosteroid standard of care, while reducing bone morbidities and mood disturbance (Guglieri et al. 2022). The clinical trials were led by the CINRG academic clinical trial network, including utilization of the CINRG coordinating center (now spun off as TRiNDS LLC), clinical evaluator training, and previous clinical studies of the CINRG network to design and adequately power the vamorolone registration study. These two studies demonstrate the key advantages to utilization of established academic clinical trial networks, inclusive of drug registration studies and coordinating centers.

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**BIOGRAPHY:** Dr. Hoffman is Professor of Pharmaceutical Sciences and Associate Dean for Research, Binghamton University – SUNY, and has co-founded and holds management positions in three academic spin-off companies focused on neuromuscular disease (CEO of ReveraGen BioPharma; Vice President of AGADA BioSciences; board member of TRiNDS LLC). Dr. Hoffman received his PhD in *Drosophila* molecular genetics from Johns Hopkins University and transitioned to human molecular genetics as post-doctoral fellow with Louis Kunkel at Boston Children's Hospital and Harvard Medical School working on the identification of the Duchenne muscular dystrophy gene and dystrophin protein. He has held faculty positions at Harvard Medical School (1988-90), University of Pittsburgh (1990-1998), George Washington University and Children's National Medical Center (1998-2016). He co-founded the Cooperative International Neuromuscular Research Group (CINRG) and has helped lead drug development programs of viltolarsen (exon skipping), and vamorolone. He is an inventor on over 20 patents and has authored over 500 publications.