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Pre-Clinical Development of an AAV Based Gene Therapy for the Treatment of Retinal Disease Due to Recessive Mutations in *GUCY2D*

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Here we present experiments leading up to an AAV based gene therapy for the treatment of retinal disease due to recessive mutations in *GUCY2D*, the leading cause of the most severe form of early-onset retinal dystrophy, Leber congenital amaurosis (LCA1). *GUCY2D* encodes retinal guanylate cyclase-1 (retGC1), a protein expressed exclusively in photoreceptor outer segments that plays a role in the recovery phase of phototransduction. Despite a high degree of visual disturbance stemming predominantly from a loss of cone photoreceptor function, LCA1 patients retain normal photoreceptor laminar architecture, except for foveal cone outer segment abnormalities and, in some patients, foveal cone loss. Adeno-Associated Virus (AAV) has emerged as the vector of choice for targeting therapeutic genes to the retina. Taken together LCA1 is an outstanding candidate for AAV mediated gene replacement therapy. Here we present IND-enabling studies conducted to evaluate 1. photoreceptor transduction mediated by an AAV5 vector containing photoreceptor specific promoter driving GFP in non-human primate (NHP), 2. the minimal effective dose using clinically representative AAV5-*GUCY2D* vector in retGC1 knock-out mice, 3. safety studies in NHP and the establishment of a no observable adverse effect level (NOAEL). Taken together, results from these studies establish a reasonable safety window for first in human clinical trials to treat LCA1.