Study treatment emergent adverse events. nightstarx limited hopes

Study NCT03116113 began in July of 2017 and looked at the safety andefficacy of AAV vector expression in patients with XLRP caused by mutation inthe RPGR-ORF15 gene.

Preclinical studies showed successful therapeutic effectof AAV vectors in proof-of-concept studies of XLRP canine models (34), and thestudies showed no toxicity in biodistribution and toxicology tests. In thisstudy, a team from the University of Pennsylvania created AAV vectors carryingRPGRorf15 cDNA and conducted an efficacy study in RPGR knock-out mouse. (35)Vectors were subretinally injected into the knockout mouse at varying doses andthey were then monitored for retinal function and changes by ERG and OCT.

Theyfound preservation of retinal structure and function both with mouse and humanRPGRor15 vector administration, and OCT showed preservation of the outer layerin vector-injected retina. Now in this human trial, 15 males 18 or older with XLRPcaused by mutations in RPGR have been recruited to be treated with a single, subretinal administration of a low dose of AAV-RPGR in the affected eye. Twoother cohorts of 5 patients each will test the medium and high doses. Successof the study will be measured by low incidences of dose limiting toxocities andincidences of treatment emergent adverse events. NightstaRx Limited hopes torelease results of this trial by 2019.

(40)Study NCT03252847 is similar to the previous trial in thatit looks at the safety and efficacy of subretinal administration of AAV withXLRP caused by mutations in RPGR. This trial, however, focuses onAAV2/5-hRKp. RPGR and compares both adults and children by recruiting 36participants of young and

adult men. They will be divided into 3 cohorts withlow, intermediate, or high subretinal dosages of the vector, respectively.

Success of the study will be measured by low incidence of adverse eventsrelated to subretinal administration of AAV-RPGR, and this safety component is definedas absence of ATIMP-related safety events; Dr. James Bainbridge at UCL andMeiraGTx hopes to release results of this trial by2020. (41)Study NCT03374657, though it doesn’t start until 2018, looks at the maximum tolerated dose of a recombinant AAV8 vector called CPK850, as determined by the single ascending dose ranging portion of the study. Theyalso want to look at the safety and potential efficacy of the vector onpossibly improving visual function in patients with RLBP1 RP due to biallelicmutations in RLBP1 gene.

They recruited 15 participants ranging in age from18-70, and formed five cohorts in ascending dosage level of the subretinalinjection to the study eye. Success of the study will be measured by low numberof participants with adverse events, serious adverse events, and deaths. It will also be measured by a high number of responders in dark adaptation. Novartis Pharmaceuticals hopes to release results of this trial by 2025. (42)Study NCT03326336, which also doesn’t start until 2018, hopes to look at the safety andtolerability of a recombinant AAV vector drug product derived from rAAV2.

7m8named GS030-DP (drug product) after being administered via intravitrealinjection and repeated light stimulation using their patented device inpatients with non-syndromic RP. This is different from all other

trials, asthey are not only studying patients with non-syndromic RP, but they arestudying intravitreal injection. Administration of AAV into the vitreous hasnot been previously successful as it is difficult for the viral vectors toreach the target bleb in the outer retinal layer, as the viscous vitreous fluidoften prevents much of the vectors from reaching the target location. Subretinal injections, however, allow for a specific injection directly intothe targeted location. Unfortunately, subretinal injection causes posteriorvitreous detachment and is many-folds more invasive of a procedure thanintravitreal injections, as the former often requires local anesthesia whereasthe latter can be done in an office setting in the period of 5-10 minutes. Thistrial recruited 18 participants ranging from 18-75 years old, and divided intofour groups, with the first three groups containing three patients each atascending dosages, and the last group containing 3-9 participants at thehighest well-tolerated dose, as determined by results from the previous threegroups.

Success of the study will be measured by thesafety and tolerability of the GS030 treatment after 1 year. GenSightBiologics hopes to release results of this trial by 2024. (43)Lastly, studyNCT033281 focuses on the safety and efficacy of AAV2/5 hPDE6B subretinalinjection in patients with RP arising from mutations in the PDE6B gene. This isthe only RP study looking at mutations in the PDE6B gene have success the studywill be measured by low incidences of ocular and non-ocular adverse events. They recruited 12 participants, all 18 years of age or older, and administeredthe lowest dose of AAV2/5-hPDE6B vector into one cohort and highest dose into thesecond

cohort. The third cohort will receive unilateral, subretinaladministration of the confirmatory dose.

Horama S. A. hopes to release resultsof this trial by 2022. (44)There have alsobeen other clinical trials not currently listed on clincialtrials. org and someof which target slightly different aspects of RP than we are focusing on. Inthe first clinical safety study (NCT01482195), six patients received submacularinjection of AAV2-VMD2-hMERTK, and three patients displayed significant improvement.

(36) Two years after treatment, however, the improvement declined and retinalthickness did not improve. In another clinical study (NCT02341807), researchersused AAV5, which has a higher tropism for photoreceptors than the previouslyused AAV2, and found improvements in retinal thickness. (37) Lastly, ciliaryneurotrophic factor (CNTF) has been studied for photoreceptor degenerationinhibition, which can delay ganglion death through AAV delivery and delayvision loss. Phase I (NCT00063765) confirmed its safety, and phase II for earlyRP (NCT00447980) and late RP (NCT00447993) are currently underway. (38) AGE-RELATED MACULARDEGENERATIONAge-related macular degeneration(AMD) is a leading cause of irreversible vision loss (visual acuity 20/2000 orworse) in the developed world.

It Different from LCA and RP, which are mainlyinherited diseases, AMD is greatly affected by older age, smoking, diet andexercise, in conjunction with race and genetics. as smoking doubles the risk Etiology: risk factors interplay tomodify the Bruch membrane/choroid complex, RPE, and photoreceptor cells. Themechanism of development is not fully understood,

but we do know the process ofneovascularization is driven by the upregulation of angiogenic cytokines, specifically VEGF.

(for wet) most likely to occur after age 50It destroys the macula (sharp, central vision)