



## Clinical Trial Overview of Investigational LUXTURNA™ (voretigene neparvovec)

Investigational LUXTURNA is currently under Priority Review with the U.S. Food and Drug Administration (FDA) for the treatment of patients with vision loss due to confirmed biallelic RPE65 mutation-associated inherited retinal disease. LUXTURNA is also under review with the European Medicines Agency (EMA) for the treatment of patients with vision loss due to Leber congenital amaurosis or retinitis pigmentosa caused by confirmed biallelic RPE65 mutations.

The safety and efficacy of LUXTURNA were assessed in two open-label Phase 1 trials, which continue to follow participants who received LUXTURNA between 2007 and 2012, and one open-label, randomized, controlled Phase 3 trial. The LUXTURNA clinical program overall includes up to four years of efficacy data from a single dose. The overall safety profile has not changed over the period of observation, and has been previously reported ([The Lancet](#) 2016; [The Lancet](#) 2017).

Following the one-year control period of the Phase 3 study, all control participants elected to cross over and received LUXTURNA; long-term safety and efficacy continue to be assessed in the Phase 3 participants who received LUXTURNA between 2013 and 2015. The clinical trial program included 41 participants with vision loss ranging from mild to advanced, and included individuals from age four to 44 years at the time of first administration. Confirmed biallelic RPE65 mutations and the presence of sufficient viable retinal cells were established in all participants.

LUXTURNA Phase 3 clinical trial data, including data from the intent-to-treat population of all randomized participants through the one-year time point, were published in [The Lancet](#). Results included in the BLA submission showed a statistically significant and clinically meaningful difference between intervention (n=21) and control participants (n=10) at one year, per the clinical trial's primary endpoint, mean bilateral multi-luminance mobility testing (MLMT) score change (difference of 1.6; 95% CI, 0.72, 2.41;  $p=0.001$ ). In addition, participants who received LUXTURNA showed a marked difference compared to control participants across the first two secondary endpoints: full-field light sensitivity threshold (FST) testing averaged over both eyes ( $p=0.001$ ) and the mobility test score change for the first injected eye ( $p=0.001$ ). A third secondary endpoint, the change in visual acuity (VA) averaged over both eyes, was not statistically significant between intervention and control participants ( $p=0.17$ ).

On average, participants in the original Phase 3 intervention group maintained functional gains observed by the day-30 visit through their last annual follow-up visit, as measured by MLMT and FST, with observation ongoing. Average improvement in FST testing observed in the original intervention group at one year was more than 100-fold (or greater than two log units).

In continuation of the trial to include crossover of the control group to receive LUXTURNA, 93 percent (27 of 29) of all treated Phase 3 trial participants saw a gain of functional vision as assessed by bilateral MLMT over the follow-up period of at least one year from administration of LUXTURNA to each eye. Additionally, 72 percent (21 of 29) of all Phase 3 trial participants receiving LUXTURNA successfully completed MLMT at the lowest light level evaluated (1 lux) at one year.

Data from a cohort of the Phase 1 clinical trial, in which investigational LUXTURNA was administered to the contralateral, or second previously uninjected eye, showed mean improvements in functional vision and visual function. This cohort of participants (n=11) received the same dose of LUXTURNA that was administered in the Phase 3 trial and would have met the Phase 3 eligibility criteria. See the publication of the three-year Phase 1 data in [The Lancet](#).

Two ocular SAEs were reported in the clinical program. There was one SAE related to the surgical procedure in one eye of a Phase 3 participant, in which there was foveal thinning and a sustained reduction in VA. One additional ocular SAE was reported in one eye of a Phase 1 participant in which the treatment for bacterial endophthalmitis led to elevated intraocular pressure and subsequent optic atrophy. There were three non-serious AEs of retinal deposits (subretinal precipitate) in three participants (three eyes) that were considered to be related to LUXTURNA. All three of these events were mild in intensity, transient in nature and resolved without consequences. No deleterious immune responses have been observed. The most common adverse reactions related to LUXTURNA reported in 10 percent or greater of the combined Phase 1 and Phase 3 trial participants included conjunctival hyperemia, cataract, increased intraocular pressure and retinal tear.

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