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US gene therapy on track to arrive with positive Luxturna vote

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Luxturna's chances of becoming the first bona fide gene therapy to win US approval look good after US FDA expert panellists voted unanimously to support a green light in patients with an inherited form of blindness.

However, investors sent the stock of its sponsor, Spark Therapeutics, up a modest 2% this morning. And, judging by the market response, any hopes that other companies in the space, including Biomarin and Uniqure, could benefit from a growing US FDA acceptance of gene therapy's risk/benefit profile have so far been largely unfounded.

Assuming that the FDA is as supportive as the advisory committee, the agency will need to consider whether very young patients can receive the agent and whether Luxturna can be injected a second time in patients whose eyesight declines after a first treatment.

On your side

Luxturna, known generically as voretigene neparvovec, aims to treat vision loss due to confirmed biallelic RPE65 mutation-associated retinal dystrophy. Patients in its pivotal trial specifically suffered from Leber congenital amaurosis – they ranged in age from four to 44, and had to have visual acuity worse than 20/60 or visual field less than 20 degrees in both eyes.

The vote was foreshadowed by benign briefing documents that focused on the meaningfulness of Spark's novel efficacy endpoint, and the safety in younger patients and those who had less severe vision loss.

Gene therapy has traditionally been associated with fears of oncogenic transformation and replication-competent virus; however, on the safety question, the FDA seemed more concerned about the risks associated with the invasive nature of the subretinal injections necessary to deliver the adeno-associated viral vector to eye tissues to trigger production of RPE65 protein.

The agency must also consider whether the visual acuity gains seen by severely impaired patients can be extrapolated to less severe ones. Spark has suggested that Luxturna be used only in patients aged three and over, although some panellists appeared willing to consider injecting into younger subjects.

Turn the lights down low

The primary endpoint, meanwhile, is called multi-luminance mobility testing, which Spark developed with input from the FDA. It essentially involves navigating a course in various degrees of darkness, with the first treated eye covered, the second treated eye covered, then both eyes uncovered, to detect whether patients could complete the test in different light levels.

In pivotal study 301, 11 of 21 patients achieved the two-level improvement. The FDA's staff asked panellists to consider the clinical relevance of such an improvement, and the 16-0 vote shows what the experts thought of it, although one did ask about functional improvement, which Spark did not measure.

The group might want to consider doing so as it nears market. Payers are going to be asked to shell out a huge price up front – between $600,000 and $1.2m, if previous gene therapies, approved in Europe, are any guide; Uniqure's Glybera cost over $1m before being withdrawn, though Glaxosmithkline's Strimvelis is priced according to a risk-sharing agreement.

Keeping children from going blind obviously has benefits, but payers will want to see data showing that doing so can avert downstream medical costs. The idea of outcomes-based pricing gained fresh importance with the recent US approval of Novartis's CAR-T therapy Kymriah, and the Swiss company's promise that payers would not be charged if a patient was not in remission at one month.

A separate point is that the FDA designated Kymriah a gene therapy even though it does not fulfil the traditional definition of such a product because it does not correct a faulty gene as such. According to the strict definition, therefore, Spark could become the first to enter the US market with a true gene therapy.

The retreatment question

The question of downstream medical costs plays into another issue: namely, retreatment in the event of failure or declines in eyesight after experiencing improvement. Ideally, a gene therapy turns on the body's protein-production engine and never requires boosting, and Luxturna has shown durable response out to four years, hence the expected high asking price – but the FDA did ask for views on repeat administration.

The panellists suggested that additional immunological data should be required before approving re-treatment. While Spark itself said that preclinical work suggested that a second dose did not increase toxicity, it acknowledged that animal studies had not predicted human responses to adeno-associated virus very well.

The risk for fading response, the nearly 50% of patients who experienced little to no improvement, and the potential for retreatment, are all issues that payers will need to consider carefully. With the FDA seemingly on board with its first gene therapy approval, it will be left to payers to sort out these questions – and they might very well ask Spark to share some of those risks.

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