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Luxturna: FDA documents reveal the value of a costly gene therapy

Jonathan J. Darrow

In 2017, the US Food and Drug Administration (FDA) approved voretigene neparvovec-rzyl (Luxturna), a gene therapy used to treat a rare form of inherited blindness. Widely described by the media as a curative treatment that 'restores vision', it was priced at US$850 000. Although voretigene neparvovec-rzyl represents a substantial therapeutic advance, most reports have failed to adequately describe study outcomes as documented by FDA reviewers. These documents reveal that the drug is not expected to restore normal vision, that only about half of treated patients met the FDA's threshold for minimally meaningful improvement, that improvements might not persist long-term, that the most common measure of visual function was rejected as a primary endpoint after yielding mixed results, and that two patients experienced permanent vision loss. Over US$100 million of additional publicly-funded costs are not evident from the US$850 000 figure.

Introduction

Voretigene neparvovec-rzyl (Luxturna) was approved by the FDA in December 2017 for the treatment of biallelic retinal pigment epithelium-specific 65 kilodalton (RPE65) mutation-associated retinal dystrophy, an inherited enzyme deficiency that generally progresses to total blindness. The treatment relies on a viral vector to deliver a normal copy of a gene that encodes a human retinal protein, the absence or dysfunction of which interrupts the visual cycle involved in the conversion of a photon of light into an electrical signal by the eye. It is administered as a one-time treatment to each eye no fewer than 6 days apart. According to the FDA, the treatment was the first directly administered gene therapy approved in the USA that targets a disease caused by mutations in a specific gene [1].

The transformative nature of voretigene neparvovec-rzyl has been widely lauded by regulators, patients, and the media. The FDA granted the drug a breakthrough therapy designation and provided priority regulatory review; in addition, the agency's Commissioner hailed the approval of the drug as a 'milestone' reflecting the 'culmination of decades of research' [1]. At a meeting of the advisory committee of the FDA, which unanimously recommended approval, one patient described how he could now see 'things that I've never been able to see before, like stars, snow falling, fireworks, but most importantly, the moon' [2]. Another explained that the postsurgical world was bright and colorful, whereas she previously saw as though she had sunglasses over her eyes while looking through a tunnel. Other patients or their family members reported improvements such as the ability to read large print rather than Braille, eat at dimly lit restaurants, use iPhone accessibility features, and see the 'faces of family and . . . some letters on the eye chart'. Parents emphasized the life-altering impact the treatment had in normalizing social interaction and enhancing academic achievement.

Media outlets reacted with similar enthusiasm. Boston's National Public Radio news station described voretigene neparvovec-rzyl as a 'miracle treatment' and the 'kind of therapeutic home run scientists have dreamed about for decades' [3]. *STAT* reported a claim by the maker of the treatment that it 'restores vision', and noted that one-time gene therapies, such as voretigene neparvovec-rzyl, are 'meant to be curative' [4]. A *Wall Street Journal* article noted

E-mail address: jjdarrow@bwh.harvard.edu.

https://doi.org/10.1016/j.drudis.2019.01.019

that, in the pivotal trial, 13 of 20 participants who received voretigene neparvovec-rzyl experienced the 'maximum possible improvement' [5]. Multiple sources stated or implied that the drug was 'curative' [6–9].

Despite the clear advance represented by the therapy, these characterizations fail to fully describe the reported benefits of the treatment, the risks and uncertainties of the procedure, or the technical challenges that remain. They also omit important details about the approval process and the outcomes that study patients actually experienced, as described by the FDA reviewers who evaluated the voretigene neparvovec-rzyl submission package. A balanced picture of the benefits, limitations, and costs of voretigene neparvovec-rzyl is important to patients seeking to become informed regarding eligibility for treatment and probable outcomes, and payors attempting to appropriately assess the value of the treatment and negotiate a fair price.

Eligibility for treatment

The *RPE65* gene is only one of more than 220 genes that, if mutated, can lead to inherited retinal dystrophies [10], accounting for an estimated 2% of cases [11]. As a result, most patients with inherited blinding conditions will not fall within the indication of voretigene neparvovec-rzyl. For those with both maternally and paternally inherited ('biallelic') mutant copies of the *RPE65* gene, the label of the drug indicates that patients must have viable retinal cells remaining. Researchers have distinguished between two pathological mechanisms of *RPE65*-associated conditions: visual dysfunction, which relates to the biochemical pathway in which the RPE65 enzyme serves as a catalyst; and photoreceptor degeneration, relating to deterioration of the cells (rods and cones) in the retina in which the biochemical processes underlying vision occurs [12]. Voretigene neparvovec-rzyl appears to address dysfunction, but it is unclear whether, or to what extent, it mitigates degeneration [13,14,15]. Given that the disease is progressive, older patients may therefore be less likely to respond as well as younger patients, or at all [14]. In addition, if photoreceptor degeneration continues to progress despite treatment, loss of visual function could eventually follow for most or all patients, thus qualifying descriptions of the drug as a 'one-time' therapy [16] that restores vision.

Efficacy measurement for voretigene neparvovec-rzyl

For those patients who respond, the treatment cannot be expected to be curative or to restore normal vision, even temporarily. The single Phase III trial supporting approval was an open-label (unmasked) trial in which 21 patients were randomized to the treatment arm and ten patients to the control arm. To assess outcomes, patients were asked to navigate a course (Fig. 1) under increasing illumination, progressing from 1 lux (equivalent to a moonless night) through 4, 10, 50, 125, 250, and 400 lux (equivalent to an office environment). A custom-designed assessment, termed multi-luminance mobility testing (MLMT) [17], was administered and points were assigned (Table 1) both before injection and at 1-year follow-up, according to the lowest light level at which a patient could accurately and with reasonable speed navigate the 5 ft × 10 ft course, which was reconfigured at each attempt. The course comprised large black arrows on the floor and required patients to avoid obstacles. For a given patient, a change in score of two points, from baseline to year 1, was considered by the FDA as the minimum change needed to demonstrate clinically meaningful benefit [15]. The mean improvement for all treated subjects was 1.9 points, compared with 0.2 points in the control arm.

The changes in score for each of the 20 treated patients and nine untreated patients (one patient in each arm withdrew consent before beginning the baseline assessment) are summarized in Fig. 2, with right-facing arrows indicating improvement in assessment score. In the control arm, 11% of patients improved by two or more points, compared with 55% in the

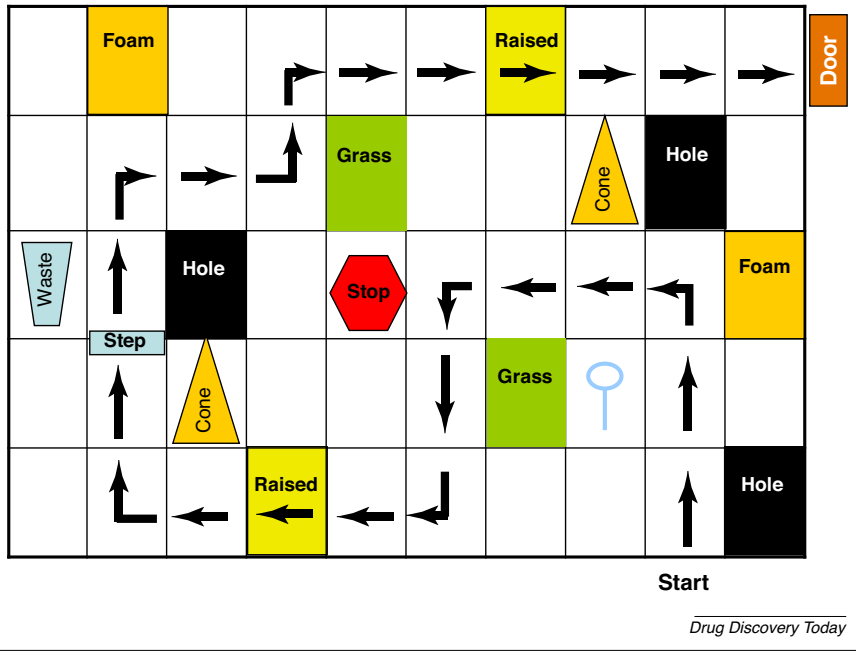

FIG. 1

Example of a navigation course used as an efficacy assessment for voretigene neparvovec-rzyl. Patients were assessed according to their ability to quickly and accurately navigate a 5 ft × 10 ft course under increasing illumination. The custom-designed assessment was reconfigured before each run and standardized for each of 12 different configurations with a fixed number of turns and obstacles. The assessment was validated for correlation with visual acuity and for inter-rater agreement of successful completion. Adapted from [17].

TABLE 1

Points assigned on successful completion of course at lowest possible lux level[a]

Lux	1	4	10	50	125	250	400	Does not pass 400
Points	6	5	4	3	2	1	0	−1

[a] Points were assigned according to the lowest illumination level at which a patient could accurately and with reasonable speed complete the course. A score of −1 indicated the patient failed the test at the brightest illumination level. A score of 6 indicated a patient passed the test at the lowest illumination level [17].

treatment arm, including 30% who improved by three or more points. Given that 13 patients in the treatment arm achieved the maximum possible score, there might have been a 'ceiling effect' to the efficacy outcomes, suggesting that the improvement could have been even greater than the assessment was able to measure. Based on Phase I results, durability of effect may be 3 to 5 years or more.

However, some treated patients, including two younger patients aged 5 and 6 years, improved by only a single point, and one patient, aged 33 years, exhibited no measurable improvement. Four (44%) of the nine control patients also improved, including one, aged 4, who improved by two points. Changes in control patient performance could be explained by natural fluctuations, variations in effort by patients, a more advanced developmental level (for younger patients) at the end of the 1-year period, or by greater experience with the assessment tool itself. Assessments were performed at baseline, at days 30, 90, and 180, and at 1 year. Given that patients used both eyes for the assessment, improvement in one eye might have masked lesser improvement or vision loss in the other eye [10], a possibility supported by single-eye assessments that demonstrated differences in improvement between the first treated eye and the second treated eye [18].

The maximum possible score of six indicated that a patient was able to recognize large black arrows and other obstacles near the patient's feet well enough to pass the MLMT at the lowest light level, and did not indicate normal vision. A passing score at any light level could be achieved by navigating a winding path totaling ~24 ft in no more than 3 min (including any time penalties assessed for errors, which ranged from 15 to 30 s per error) and committing no more than three errors. Score interpretation was also made more challenging, as some advisory committee members observed, because the scoring system was ordinal whereas the corresponding lux levels were logarithmic and unevenly spaced (with steps ranging from a change of 0.25 log units to 0.6 log units), meaning that a two-point change in the ordinal scale could carry a different meaning depending on the starting score.

Notably, the trial sponsor decided not to use as a primary endpoint a more traditional measure of vision function [logarithm of the minimum angle of resolution (logMAR) improvement of 0.3 or more] after an earlier trial yielded mixed results: a 5-year follow-up of Phase I patients showed that a greater proportion of treated than untreated patients improved by logMAR 0.3 or more (46% versus 16%), but also that a greater proportion worsened by logMAR 0.3 or more (16% versus 0%), making the results 'difficult to interpret' [15]. The pivotal trial included logMAR as a secondary efficacy measure and demonstrated a numerical advantage to treatment (logMAR change at year 1 of −0.16 in the treatment arm versus +0.01 in the placebo arm, where more negative values indicate improvement), but the difference was not statistically significant.

Safety concerns are unlike most FDA-regulated medicines

Voretigene neparvovec-rzyl is unlike most FDA-approved injectable treatments in that administration requires a surgical procedure. The gene therapy is administered by subretinal injection under general anesthesia, supplemented with local anesthesia ('retrobulbar anesthetic irrigation') [10]. It involves cutting into the covering of the white of the eye ('conjunctival peritomy'), cutting through the layer below ('Tenon's capsule dissection'), removal of the vitreous gel of the eye ('pars plana vitrectomy'), removal of membrane (if present) in the macular area using a scraper and forceps, insertion of a tube ('39-gauge hydrodissection cannula') through which the drug is administered by subretinal injection, and potential repair of retinal breaks, if any.

The FDA reviewers combined the safety data from the Phase III study with an earlier Phase I study, yielding a total of 41 treated patients (control patients in the Phase III trial crossed over to receive treatment after 1 year). Based on a follow-up period ranging from 1 to 6 years, two (5%) treated patients experienced wrinkling on the surface of the macula ('maculopathy'), three (7%) experienced macular holes, four (10%) experienced retinal tears, six (15%) experienced increased intraocular pressure, and eight (20%) experienced clouding of the lens ('cataract'), among other treatment-related ocular adverse events. Overall, 27 (66%) treated patients experienced one or more ocular adverse events, which were primarily attributed to the surgical procedure rather than to the drug itself. Most were mild or moderate and resolved, or were ongoing but consistent with disease progression irrespective of treatment [10,15]. However, two (5%) study participants sustained permanent vision loss attributed to the subretinal administration procedure [15,19], including irreversible optic atrophy because of sustained increased intraocular pressure associated with the administration of ocular steroids for the treatment of *Staphylococcus* infection, and permanent loss of central vision in the right eye from 20/150 at baseline to 20/320 because of injection-related macular thinning [15]. A 15-year follow-up study to assess long-term safety and efficacy is ongoing.

Voretigene neparvovec-rzyl is the first FDA-approved therapy to rely on an adeno-associated virus (AAV) vector as its delivery mechanism, although more than 100 clinical trials have used such vectors [20] and one AAV vector-based gene therapy (alipogene tiparvovec, Glybera) was approved in Europe in 2012 before being withdrawn for commercial reasons [21,22]. These engineered vectors are considered to be nonpathogenic and are not expected to insert into the host genome, reducing the risk of cancer mutagenesis [23,24]. FDA reviewers expressed concern over potential liver toxicity based on unrelated trials of intravenously administered AAV vector-based therapies, but observed that immune reactions were mild at all doses in the Phase I and III studies of voretigene neparvovec-rzyl.

Personal and societal costs of voretigene neparvovec-rzyl

The maker of voretigene neparvovec-rzyl, Spark Therapeutics, priced the drug at US$850 000, or US$425 000 per eye, which does not include the cost of surgery (estimated at US$4876 [20]) or other medical costs. Spark's Chief Executive Officer explained this price was justified by the value of the drug to patients, including the value of being able to work and reduced caregiving needs, in addition to the more obvious quality-

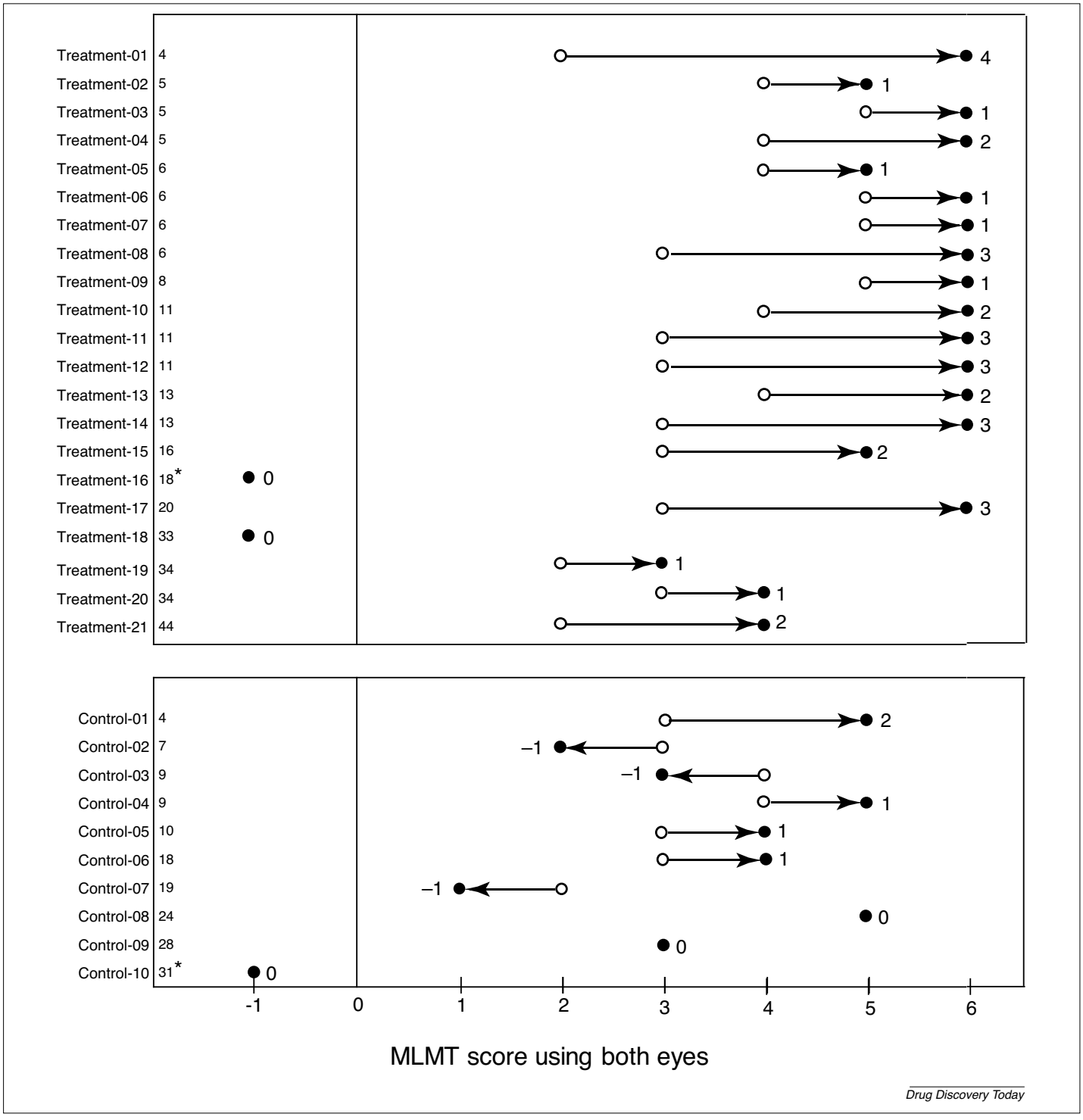

FIG. 2

Changes in score from baseline to 1-year for all treated and control patients. Patients were evaluated for each eye separately (i.e., with one eye patched) and for both eyes together. Results of the change in score from baseline to year 1 using both eyes are presented. The numbers adjacent to each data point or arrow head indicate the change in score. The numbers to the right of each patient number indicate patient age at randomization. Treatment 16 did not receive treatment; Control 10 withdrew consent. Course navigation (as described in Fig. 1) was evaluated at seven specified illumination levels, measured in lux, and points awarded according to the lowest illumination level at which successful completion occurred, as determined by trained, masked evaluators who reviewed video recordings of subject assessments. The assessment was repeated for at least two illumination levels (one failing, one passing) [15]. Adapted from [18].

of-life improvements [25]. By contrast, the Institute for Clinical and Economic Review (ICER), a nonprofit healthcare research organization that provides independent cost-benefit analysis of pharmaceutical products, estimated that treatment cost would have to be lowered from US $850 000 to between US$214 553 and US $755 633 to be cost-effective for those patients 3-years old at the time of treatment, under varying assumptions regarding cost savings and using commonly cited thresholds of US$50 000 and US$100 000 per quality adjusted life year

(QALY) [20,26–27]. For those 15-years old at the time of treatment, costs would have to be lowered to between US$88 499 and US $362 524. Cost-per-QALY thresholds are controversial [28,29], and ICER also included less commonly cited thresholds in its analysis.

Given that the calculations by ICER assumed that measured benefits would persist for 10 years and that patients would experience an additional 10-year period during which effects waned, these cost–benefit figures might rise or fall if treatment effect duration is ultimately demonstrated to be shorter or longer. FDA reviewers cited evidence that progressive cellular degeneration might occur within 1–3 years notwithstanding sustained improvement in visual function in studies of similar AAV vector-based gene therapies for the identical indication [13,15,30]. Benefit might also be higher than calculated because, according to ICER, certain quality-of-life benefits might not have been adequately captured in its analysis because of data limitations. The US$850 000 cost also does not reflect confidential rebates that insurers might be able to negotiate, or outcomes-based rebates that Spark has announced it will offer if the drug does not reach certain effectiveness thresholds in particular patients as determined at approximately 3 months and 2.5 years after treatment [16].

Despite high costs, patients might pay little or nothing out of pocket beyond their insurance premiums. Spark has stated that it will help with travel, accommodation, and other costs, and that commercially insured patients can expect to bear 'zero cost' for voretigene neparvovec-rzyl and immediate follow-up care [16]. Spark has also offered physicians free *RPE65* genetic test kits to determine whether their patients meet the FDA-labeled indication. Experts and study patients who offered testimony at the Advisory Committee meeting reported that Spark had already provided financial support for their travel and accommodation, and similar support will be provided to patients to facilitate travel to one of the small number of treatment centers in the USA that will offer the procedure [6]. These subsidized costs can be substantial. One patient, for example, reported that Spark Therapeutics agreed to pay US$4000 in out-of-pocket costs [5].

Although patients might experience meaningful benefit while being spared from immediate financial burdens, these benefits are not without cost. The price of voretigene neparvovec-rzyl (minus expenses saved) must eventually be passed along in the form of higher insurance premiums. If all of the ~1000–3000 patients in the USA estimated to fall within the indicated population receive the US$850 000 treatment [31], expenditures could total between US$850 million (i.e., 1000 × US$850 000) and US$2.55 billion (3000 × US$850 000), not including hospital costs.

Less-apparent costs must also be considered. Given that it is indicated for a rare disease, voretigene neparvovec-rzyl was granted an orphan drug designation, making Spark Therapeutics potentially eligible for a tax credit worth 50% of its clinical testing costs under the 1984 Orphan Drug Act (reduced to 25% in 2018) and entitling it to a waiver of the over US$2 million new drug application fee [32]. Any patient out-of-pocket costs paid for by the manufacturer are also likely to qualify as deductible business expenses and, therefore, represent an additional indirect government subsidy borne by all taxpayers. Under the 2012 FDA Safety and Innovation Act, Spark Therapeutics was also awarded a rare pediatric disease priority review voucher [33] that it sold in 2018 for US$110 million [34]. Potentially of greater significance, as more gene therapies are approved, the launch price of voretigene neparvovec-rzyl will anchor the price of treatments that address indications affecting larger numbers of individuals. Finally, some therapies might be widely prescribed off-label, potentially increasing costs while providing uncertain benefit.

Implications

Issues of cost, benefit, and uncertainty will become increasingly important as a wave of costly new therapies tested in small patient populations are developed and approved. In 2018, 58% of new drugs addressed orphan indications, defined as those affecting fewer than 200 000 patients in the USA, compared with 39% the year before [35]. Gene therapies, which are targeted to specific genetic abnormalities, are likely to address especially small patient populations and remain among the costliest drugs. Although small trials might be unavoidable for such indications [36,37], limited evidence and uncertain long-term benefits and risks will complicate coverage decisions and could lead to overpayment if benefit and risk profiles turn out to be less favorable than expected. The increasing prevalence of high-priced rare disease treatments also creates challenges for payors, particularly smaller ones, who might experience difficulty forecasting annual claim amounts.

Concluding remarks

The technical advance underlying voretigene neparvovec-rzyl represents a scientific milestone, and the gene therapy offers improved visual function and meaningful therapeutic benefit to patients who previously had few options. Contributions to the medical toolbox such as this should be appropriately incentivized, including via adequate financial compensation to their makers, taking into account other healthcare imperatives that must also be funded. Although voretigene neparvovec-rzyl represents a more substantial step forward than most other costly interventions introduced each year (a low bar, given that many offer little or no incremental benefit [38–40]) and deserves a proportionally larger reward, it is well short of the cure that patients desire. Patients, payors, and policymakers should be aware of the risks and limits of the effectiveness of the technology, the incomplete and short-term nature of the evidence, and the various nontransparent subsidies that its manufacturer was eligible to receive as they consider treatment options, make reimbursement decisions, and evaluate incentives to promote the development and availability of new pharmaceutical products, including gene therapies.

Declaration of interest

J.J.D. is supported by grants from the Laura and John Arnold Foundation, the Harvard-MIT Center for Regulatory Science, and the Engelberg Foundation. The funders had no role in the conception, preparation, or approval of the manuscript, or in the decision to submit the manuscript for publication.

Acknowledgements

The author gratefully acknowledges Jason Comander, Aaron Kesselheim, Nicole Lemanski, David Rind, and Melissa Hergan Simmons for their input on earlier drafts.

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Jonathan J. Darrow

Program on Regulation, Therapeutics, and Law (PORTAL), Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, 1620 Tremont St, Suite 3030, Boston, MA 02120, USA