

Title: Comparison of the United Kingdom and United States Approaches to Approval of New Neuromuscular Therapies

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## **Abstract**

Many novel therapies are now available for rare neuromuscular conditions that were previously untreatable. Hereditary transthyretin amyloidosis and spinal muscular atrophy are two examples of diseases with new medications that have transformed our field. The United States and the United Kingdom have taken disparate approaches to the approval and coverage of medications despite both providing incentives to develop therapies targeting rare diseases. The United States requires less evidence for approval when compared to medications for common diseases and does not have a mechanism to ensure or even encourage cost-effectiveness. The Institute of Clinical and Economic Review provides in depth cost-effectiveness analyses in the United States but does not have the authority to negotiate drug costs. In contrast, the United Kingdom has maintained a similar scientific threshold for approval of all therapies, while requiring negotiation with National Institute for Health and Care Excellence to ensure that medications are cost-effective for rare diseases. These differences have led to approval of medications for rare diseases in the United States that have less evidence than required for common diseases. Importantly, these medications have not been approved in the United Kingdom. Even when medications meet traditional scientific thresholds, they uniformly arrive with high list prices in the United States, whereas they are available at cost-effective prices in the United Kingdom. The main downsides to the United Kingdom approach are that cost-effective medications are often available months later than in the United States and some medications are unavailable.

Key Words/Phrases: Orphan Drugs, Rare Disease, Cost-effective, Neuromuscular Disease

## **Introduction**

The United States (US) recognized the need to incentivize treatments for rare diseases in the early 1980s, specifically naming amyotrophic lateral sclerosis (ALS) and muscular dystrophy as two conditions (among many) lacking available treatments.<sup>1</sup> The European Union (EU), of which the United Kingdom (UK) was a member until recently, followed suit in 1999, passing legislation to encourage development of treatments for rare diseases stating that “patients suffering from rare conditions should be entitled to the same quality of treatments as other patients.”<sup>2</sup> These pieces of legislation paved the way with significant incentives to pharmaceutical companies to develop and bring to market treatments for these rare diseases. There is little doubt that these incentives have led to more therapies for patients with rare diseases and financial benefits to pharmaceutical companies. Orphan drug sales currently total ~ 140 billion dollars (~15% of total worldwide pharmaceutical sales) per year with expected exponential growth over the next several years.<sup>3</sup> Rare diseases affect only ~3.5-5.9% of the population, signifying that pharmaceutical companies make a disproportionate amount of money on orphan drugs compared to other medications.<sup>4</sup> Importantly, the US and UK have developed divergent approaches to medication approval and coverage for rare diseases resulting in fundamental differences in the availability of medications and costs of treatment. This article will summarize the two different approaches while also providing examples of how these approaches have affected availability and cost of new neuromuscular therapies in the two countries.

## **The United States Approach**

The Orphan Drug Act in 1983 provided a financial incentive for pharmaceutical companies to develop and bring to market novel medications for rare diseases based on a prevalence of less than 200,000 individuals in the US (~60 cases per 100,000 individuals).<sup>1</sup> The law provides market exclusivity for 7 years compared to the usual 5 years for medications, while also providing tax credits on clinical trials, availability of federal subsidies for clinical trials, and reduced or waived regulatory fees.<sup>5</sup> In order to achieve orphan designation, pharmaceutical companies are required to prove scientific rationale and

disease prevalence. The US currently has over 5,500 medications approved under orphan drug status.<sup>6</sup>

Patients with severe, life threatening diseases that lack good treatments are often willing to accept more cost and risk to try novel treatments, even if efficacy data is limited and costs may be high. In response to pleas from advocates for patients with rare diseases and a desire to increase available treatments, the US Food and Drug Administration Safety and Administration Act (FDASIA) was signed into law in 2012. This law expanded the ability of the Food and Drug Administration (FDA) to assist pharmaceutical companies in the development and subsequent FDA review of “breakthrough therapies” with preliminary evidence supportive of substantial improvement over currently available therapies for patients with serious or life threatening diseases.<sup>7</sup> Goals of the FDASIA were to promote innovation, increase stakeholder involvement, and enhance the safety of the drug supply chain. The approval process has evolved over many years, with the FDA requiring less data, encouraging use of surrogate measures, and shortening the review time for approval of treatments for rare diseases. In fact, nearly half of new drug approvals are based on a single clinical trial, instead of the two or more that used to be the standard.<sup>8</sup> While this has significantly shortened the time to approval for new therapies, it has also demonstrated the FDA’s willingness to approve medications with less efficacy data and use of surrogate measures rather than survival or improved patient outcomes. The benefits of earlier access to a medication must be weighed with the potential that patients will be exposed to medications that have less favorable benefit to risk profiles than anticipated or even to medications that are not efficacious.<sup>9</sup> Additionally, there is increasing evidence of pharmaceutical company abuse of the Orphan Drug Act through repurposing of already available medications for narrower indications to gain the lucrative protections and exclusivity benefits afforded to orphan drugs.<sup>10</sup> The US approach to orphan drug approval has led to a lower scientific standard compared to that used for medications for common diseases.

The FDA has no role in determining pricing of a pharmaceutical product before or after approval and there are no universal mechanisms to guide sustainable health system costs. One shortcoming of the US healthcare system is the inability to control costs of therapies.<sup>11</sup> The Institute of Clinical and Economic Review (ICER) was founded in 2006 as an independent, non-partisan group to objectively evaluate prescription medications within the framework of “health-benefit price benchmark” with an ultimate goal of helping the US evolve towards a system of fair pricing, equal access, and a sustainable health system. ICER uses the quality-adjusted life year (QALY) as a measure of disease burden accounting for the quality and quantity of life lived as a measure of health effectiveness vs. cost-effectiveness.<sup>12,13</sup> However, the use of QALYs in rare disease is challenged by several factors including: limited long term effectiveness data in young populations with previously untreatable conditions, shorter duration clinical trials with limited randomized or head to head trials, and difficulties in measuring the burden of illness on family caring for children.<sup>14,15</sup> The ICER Value Assessment Framework takes into account the long term value and the short term affordability with a health-benefit price benchmark of \$100,000-\$150,000 per QALY. However, it should be noted that this threshold is subjective and may not fully account for the value of novel therapies for rare diseases.<sup>13</sup> ICER provides this information to key stakeholders including drug manufacturers, patient advocacy groups, provider groups, government entities and health insurance plans. The FDA approval of treatments for rare diseases considers only the scientific evidence for efficacy and safety and does not consider ICER guidelines or cost effectiveness of novel medications. Once approved, medications are priced by the pharmaceutical company. Given that cost-effectiveness is not considered, the US approach to orphan drug approval has led to availability of many novel therapies at high list prices (Figure 1).

### **The United Kingdom Approach**

The EU passed legislation in 1999 with the goal of increasing development and availability of novel medications for rare diseases.<sup>2</sup> The EU allows for 10 years of market exclusivity and uses a prevalence of

5 per 10,000 individuals in the European community for orphan drugs. In addition to the requirement of the treatment indication for a rare disease, the EU requires that the condition is considered life threatening or seriously debilitating *and* that there is no satisfactory current method of diagnosis, prevention or treatment. This distinction provides a slightly higher bar to qualify for orphan drug status compared to the US. The EU has over 100 approved orphan drug therapies for rare diseases.<sup>16</sup> The European Medicines Agency (EMA) is the primary regulatory and approval agency for medications in the EU including the UK until very recently. Similar to the FDA, the EMA has also received more frequent submissions without high quality randomized controlled trials but approves fewer medicines and takes longer to approve when they do.<sup>17</sup> The UK approach to drug approval for rare diseases has led to a similar scientific standard compared to that used for approval of medications for common diseases.

Once the EMA approves a medicine for use, it receives a marketing authorization; however, it is not commercially available until additional decisions on pricing are made. In the UK, the pharmaceutical company must then submit data to the National Institute for Health and Care Excellence (NICE) for cost-effectiveness evaluation. Based on review of the evidence for impact and an incremental cost-effectiveness ratio of below £100,000 per QALY, NICE then determines whether to recommend the medication.<sup>18</sup> If recommended, then the medication will be covered under the National Health Service (NHS) constitution; however, if a medication is not recommended then it is not available on formulary and the company will need to resubmit an application with a lower cost of treatment. This process often leads to a period of negotiation between the pharmaceutical company and NICE during which the medication is approved, but not available in the UK. The UK approach to the cost of drugs for rare diseases has led to the approval and availability of only cost-effective medications although sometimes with a delay of months while negotiations occur (Figure 1). One downside to this approach is that medications which may be clinically effective, but are not cost effective, are unavailable for treatment of neuromuscular diseases. Another downside is the delay from EMA approval to availability for clinical

use. We will now provide examples of new neuromuscular therapies to demonstrate how the US and UK approaches have led to key differences in approval, cost-effectiveness, and availability of these medications.

### **Hereditary Transthyretin Amyloidosis:**

Until recently, hereditary transthyretin amyloidosis (hATTR) had few treatments aside from liver transplant. Phase 3 trials for patisiran and inotersen were published in 2018.<sup>19,20</sup> The APOLLO study was a phase 3, randomized, controlled trial comparing patisiran with placebo and demonstrated a clinically significant difference in the modified Neuropathy Impairment Score +7 score at 18 months as well as secondary measures of the Norfolk Quality of Life-Diabetic Neuropathy scale and 10-m walk test.<sup>19</sup> The Neuro-TTR trial was a phase 3, randomized, controlled trial of inotersen over a 15-month period which also demonstrated a clinically significant difference in the mNIS+7.<sup>20</sup> An indirect comparison showed that patisiran appears to demonstrate higher efficacy than inotersen.<sup>21</sup>

The FDA approved patisiran in Aug 2018 and inotersen in October 2018.<sup>22,23</sup> Patisiran and Inotersen were both priced at \$450,000 annually in the US. However, ICER cost analysis, using a threshold of \$150,000 per QALY, indicated that inotersen should be priced at \$25,379 annually and patisiran at \$46,488 annually for each treatment to be considered cost-effective (Table 1).<sup>24</sup>

The EMA approved patisiran in Aug 2018 and inotersen in July 2018.<sup>25,26</sup> In the UK, the initial list price for both treatments was £300,000. However, NICE declined coverage at this cost and both pharmaceutical companies were required to negotiate a confidential commercial agreement to achieve a lower acceptable cost per QALY gained (between £80,730 and £125,256 per QALY for patisiran and £96,697 per QALY for inotersen).<sup>27-30</sup> Agreement was reached with NICE in July of 2019 for patisiran and April of 2019 for inotersen.



The US and UK approaches both led to approval of these highly effective therapies, but in the US, the medications have high retail prices whereas in the UK the medicines are available at cost-effective prices. The downside to the UK approach is that there was an initial delay in availability of patisiran and inotersen of 9-11 months compared to the US (Table 2).

### **Spinal Muscular Atrophy**

The most severe form of spinal muscular atrophy (SMA) demonstrates progressive loss of motor function and is universally fatal without recently available treatments.<sup>31</sup>

Nusinersen is an antisense oligonucleotide drug that modifies pre-messenger RNA splicing of the SMN2 gene and subsequently promotes increased production of full-length SMN (spinal motor neuron) protein. Multiple randomized phase 3 trials, including ENDEAR and CHERISH, demonstrated significantly improved motor milestones and event free survival.<sup>32,33</sup>

Mendell et al. studied the effects of functional replacement of the mutated *SMN1* gene using a single dose of intravenous adeno-associated virus vector, known as onasemnogene abeparvovec.<sup>34</sup> 15 patients with SMA1 were included in this Phase 2 trial with the primary outcome of safety, and secondary outcome of time until death or permanent ventilator assistance. Impressively, all 15 patients were alive and event-free at 20 months of age, when compared to 8% survival rate in a historical cohort.<sup>34,35</sup> Given the natural history of SMA is never sitting and a 90% fatality rate at 2 years of age, the fact that 11 of 15 treated patients regained head control and independent sitting and 2 regained the ability to walk for years is remarkable. The therapy proved to be safe in this small study, showing only elevated serum aminotransferase levels without other liver enzyme abnormalities that was attenuated by prednisolone treatment. A phase three trial has not been completed.

Risdiplam is a small molecule SMN2 splicing modifier that binds two sites in SMN2 pre-messenger RNA which results in correcting the splicing deficit of SMN2 and subsequently increased levels of full-length SMN protein. Risdiplam was studied in 180 non-ambulatory patients with SMA2 (71%) and SMA3 (29%). Risdiplam demonstrated a clinically meaningful and statistically significant difference in motor function compared with placebo.<sup>36-38</sup>

Nusinersen, onasemnogene abeparvovec, and risdiplam were approved by the FDA in December 2016, May 2019, and August 2020 respectively.<sup>39-41</sup> ICER evaluated the use of nusinersen and onasemnogene abeparvovec in SMA.<sup>42</sup> They noted nusinersen does not meet traditional cost-effectiveness thresholds in any population. Their review noted nusinersen to be more cost-effective in the pre-symptomatic population, but even in this population the cost would have to be reduced to below \$65,000 per year to meet a \$150,000 per QALY threshold. In later-onset SMA, nusinersen cost over \$8 million per QALY gained given that there is no evidence to demonstrate life extension in this population and the benefits of treatment translate to only small improvements in QOL compared to best supportive care. Onasemnogene abeparvovec also failed to meet established cost-effectiveness thresholds (\$247,000 per QALY) but was much closer to cost-effectiveness than nusinersen (Table 1). The efficacy of onasemnogene abeparvovec is only based on a single small phase two study.

The EMA approved nusinersen and onasemnogene abeparvovec in May 2017 and May 2020 respectively, though onasemnogene abeparvovec is authorized for use in the EU under ‘conditional authorization’, which means the company will be required to provide new evidence and the EMA will review this information annually.<sup>43,44</sup> Risdiplam is not currently authorized for use by the EMA, but in February 2019 it was granted orphan designation.<sup>45</sup> NICE concluded that nusinersen should be recommended as an option for treating pre-symptomatic and symptomatic SMA types 1, 2 and 3.<sup>46</sup> Onasemnogene abeparvovec appears to be on the cusp of formal approval by NICE for use in the UK.<sup>47,48</sup>

The US and UK approaches both led to approval of nusinersen and onasemnogene abeparvovec, whereas risdiplam is only approved in the US. All three medications are available in the US. Only nusinersen is currently available in the UK, although onasemnogene abeparvovec is approved by the EMA, undergoing NICE appraisal and may be available soon. Access to these medications occurred months earlier in the US, but the UK appears to have negotiated a cost for nusinersen that will support long term cost-effectiveness and availability. Moreover, patients with SMA in the UK lack current access to onasemnogene abeparvovec and risdiplam (Table 2).

### **Duchenne Muscular Dystrophy**

Duchenne muscular dystrophy (DMD) presents in early childhood as progressive muscle weakness associated with cardiopulmonary complications which has only had glucocorticoids available as treatment for many years.<sup>49,50</sup>

A randomized control trial comparing deflazacort, prednisone, and placebo demonstrated that deflazacort and prednisone were superior to placebo over 12 weeks in measurements of muscle strength and functional measures.<sup>51</sup> Participants were then randomized to receive either deflazacort or prednisone for an additional 40 weeks. No differences in strength or function were observed, but deflazacort was associated with less weight gain and psychiatric adverse events, while cataracts and growth delays were more frequently reported.

Several novel therapies have recently become available, including exon skipping therapies that result in dystrophin restoration (eteplirsen, golodirsen, viltolarsen). Exon skipping therapies are known as phosphorodiamidate morpholino oligomers (PMOs) which are designed to bind to pre-mRNA, alter splicing process and skip the targeted exon from the mature mRNA sequence with a goal of increasing

dystrophin expression.<sup>52,53</sup> A 12 week open-label phase 2 study evaluated the safety and tolerability of eteplirsen in 19 ambulatory DMD patients between ages 5 and 15 years with a deletion amenable to exon 51 skipping therapy. There were no clear drug-induced adverse events, and the secondary outcome revealed a dose-dependent significant increase in dystrophin expression.<sup>54</sup> A subsequent 48-week study randomized DMD boys with amenable deletions to exon 51 skipping to 30 or 50 mg/kg eteplirsen or placebo for 24 weeks.<sup>55</sup> After 24 weeks, patients on placebo were switched to either receive 30 or 50 mg/kg eteplirsen in an open-label extension study in which muscle biopsies were obtained before treatment and at 48 weeks. Eteplirsen treatment resulted in significant improvement in dystrophin expression in muscle biopsies and improved 6-minute walk test compared to patients who were initially on placebo.<sup>56</sup> Golodirsen and viltolarsen induce exon 53 skipping and have also demonstrated increased dystrophin staining after treatment without evidence of improvement in patient-oriented outcomes in randomized trials.<sup>57,58</sup>

Importantly, none of the PMOs have undergone a phase 3 trial to evaluate clinical effectiveness, and most recent studies have included a significant open label period without blinding. Outcome measures have included evaluation of pre- and post-treatment dystrophin expression in muscle and comparisons to historical cohorts.

In the US, all the above therapies are now available. Deflazacort was approved by the FDA in February 2017 to treat patients age 5 years and older with DMD.<sup>59</sup> The FDA granted accelerated approval of the above exon skipping therapies based on the surrogate endpoint that is thought to predict clinical benefit, though the FDA is requiring the pharmaceutical companies to conduct a clinical trial to confirm each treatment's clinical benefit with a threat that if they do not verify clinical benefit, the FDA may initiate proceedings to withdraw approval of the therapy.<sup>60-62</sup> ICER evaluated the long-term cost-effectiveness of the above therapies, and noted that the annual treatment cost for a 40 kg patient was noted to be \$550 for

prednisone, \$81,400 for deflazacort, and \$1,002,000 for eteplirsen.<sup>63</sup> The incremental cost-effectiveness ratios comparing deflazacort to prednisone (\$361,000 per QALY) is beyond the range of commonly accepted thresholds of \$50,000 to \$150,000 per QALY despite favorable assumptions about treatment effects (Table 1). With regards to eteplirsen and golodirsen, a value-based price estimate was not available given the absence of evidence proving clinical benefit. At current pricing, the PMOs are not cost effective even assuming positive effects on clinical outcomes.

Eteplirsen was not approved by the EMA in May 2018, and again in September 2018 after reexamination. The EMA cited that the Committee for Medicinal Products for Human Use (CHMP) was concerned that the study only involved 12 patients, did not compare treatment versus placebo beyond 24 weeks, there was no meaningful difference between eteplirsen and placebo in the 6 minute-walk test, and the methods for comparing results of the studies with historical data was not satisfactory for showing effectiveness.<sup>64</sup> Similarly, golodirsen and viltolarsen have not been approved by the EMA.

In summary, the US approach has led to the approval of deflazacort and the PMOs. Deflazacort has comparable efficacy to prednisone, but is not cost-effective. The evidence for PMOs is based on surrogate markers of disease, therefore, the evidence does not meet traditional scientific thresholds. The UK approach has prevented access to deflazacort and PMOs (Table 2).

### **Amyotrophic Lateral Sclerosis**

ALS has long attracted intense interest from researchers to develop effective therapies. Edaravone, a free radical scavenger, was initially developed for use in acute ischemic stroke in Japan in the early 2000's.<sup>65</sup> The first phase III trial failed to show a significant difference in the primary end point of the Revised Amyotrophic Lateral Sclerosis Rating Scale (ALSFRS-R) between the treatment and placebo groups.<sup>66</sup> A post-hoc analysis of a subpopulation of well-defined early stage ALS patients without respiratory

involvement suggested a possible benefit.<sup>67</sup> Using strict inclusion criteria, another phase III trial demonstrated a small, statistically significant slowing in the rate of decline, however a higher proportion of patients in the placebo arm were in stage 2 ALS, indicating more severe disease at time of enrollment.<sup>68</sup> Edaravone places significant burden on ALS patients and care givers with the need for port placement, time commitment for frequent infusions and transportation to infusion centers (though infusions can be done at home for some patients) that are difficult to measure.<sup>69</sup> However, other adverse events were rare in the clinical trials.<sup>70</sup>

Edaravone was approved by the FDA for treatment of all patients with ALS in May 2017 under the orphan drug designation.<sup>71</sup> ICER has not yet published a review of edaravone. However, the Canadian Agency for Drugs and Technologies in Health (CADTH) published a Common Drug Review (CDR) for edaravone in 2019 finding that edaravone likely increases life expectancy by two to five months and increases quality-adjusted life expectancy by one to three months, similar to riluzole.<sup>72,73</sup> However, the incremental cost-effectiveness ratio for edaravone compared to current standard of care was \$1,957,000 per QALY gained and would need to be reduced in price by ~97% to be cost-effective (Table 1).

The manufacturer of edaravone filed for approval in the EU via the EMA but ultimately withdrew the applications. At the time of EMA withdrawal in May 2019, the CHMP provisional opinion was that edaravone could not have been approved, citing the following concerns: 1) the drug's lack of demonstrated efficacy to increase median survival, breathing, and muscle strength 2) selection of stage 1 & 2 ALS patients in the phase III trial 3) no improvement in patients switched from the placebo group to the edaravone group and 4) short duration (24 weeks) for assessment of primary endpoint. The CHMP held the opinion that the benefits of edaravone did not outweigh its risks due to lack of proven effectiveness.<sup>74,75</sup>

In summary, the US approach has led to the approval and widespread availability of edaravone, which has one positive and one negative clinical trial, potential harms related to frequent intravenous infusions, and high costs contributing to complex treatment discussions between providers and ALS patients.<sup>76</sup> In contrast, the UK approach has not allowed access to edaravone until further studies are performed to establish efficacy and cost-effectiveness (Table 2).

### **Myasthenia Gravis**

Myasthenia gravis (MG) has many effective therapies, however an estimated 10-15% of all cases are considered refractory and do not respond to typical therapies such as pyridostigmine, corticosteroids, steroid-sparing agents, or require ongoing intravenous immunoglobulin or plasma exchange.<sup>77</sup>

Eculizumab is a humanized monoclonal antibody against human complement component 5 (C5) protein, which inhibits terminal formation of the membrane attack complex and destruction of the post-synaptic muscle membrane. The randomized, double-blinded REGAIN phase 3 trial comparing eculizumab to placebo failed to meet its primary efficacy endpoint of change in the Myasthenia Gravis Activities of Daily Living (MG-ADL) total score after 26 weeks.<sup>78</sup> However, most other pre-specified secondary efficacy endpoints, including change from baseline Quantitative Myasthenia Gravis (QMG) score, were significantly improved compared to placebo. The open-label REGAIN extension study demonstrated improvement in mean MG-ADL score and a considerable number of patients achieved minimal manifestation of disease status.<sup>79</sup> Despite REGAIN not meeting its primary efficacy endpoint, the positive results on several secondary measures and the results of the open label extension trial indicate that eculizumab likely has a role for refractory AChR antibody-positive generalized MG patients.

The FDA approved eculizumab for myasthenia gravis in October 2017. Cost is currently a barrier for use of eculizumab in refractory generalized MG patients, given its list price of approximately \$500,000 per

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patient per year.<sup>80</sup> ICER has not performed a cost-effectiveness evaluation to date. However, CADTH analysis of eculizumab is associated with an ICER of \$1,505,712 per QALY gained and has a 0% probability of being cost-effective at current cost.<sup>81</sup>

The EMA approved eculizumab for myasthenia gravis in Aug 2017.<sup>82</sup> However, the pharmaceutical company has not submitted an evidence submission to NICE and thus eculizumab had its appraisal terminated.<sup>83</sup> As a result, eculizumab is not available in the UK for refractory, generalized myasthenia gravis.

In conclusion, the US and UK approaches both led to approval of this likely effective therapy for refractory MG. In the US, eculizumab is available, but its high list price likely means that it is not cost-effective. In the UK, physicians do not have access to a potentially effective option for refractory myasthenia gravis when other options fail, but the health system avoids the high costs of this medication (Table 2).

### **Lambert Eaton Myasthenic Syndrome**

3,4-diaminopyridine (3,4-DAP, amifampridine), a potassium-channel blocker, has been the mainstay of treatment for Lambert-Eaton myasthenic syndrome (LEMS) for nearly 40 years. Several randomized controlled trials (RCTs) have demonstrated that 3,4-DAP is safe and significantly improves QMG score, isometric muscle strength, and compound muscle action potential amplitudes on electrodiagnostic testing in LEMS patients.<sup>84-86</sup> A 2011 Cochrane review concluded there was moderate to high quality evidence to support the use of 3,4-DAP in LEMS patients.<sup>87</sup> Two RCTs of amifampridine, a phosphate salt form of 3,4-DAP, demonstrated significant improvement in baseline QMG score and Subjective Global Impression score without serious adverse effects.<sup>88,89</sup>



3,4-DAP was initially available in the US and UK through compounding pharmacies under a “compassionate use” Investigational New Drug program. The base form was relatively inexpensive—previously available at a cost of ~ \$1600 per year. The FDA approved amifampridine in 2018 with orphan drug status.<sup>90</sup> Amifampridine was then priced at \$375,000 / year in the United States, a 23,000% increase compared to the prior annual cost.<sup>91</sup> A cost-effectiveness analysis is not yet available from ICER.

In 2009, the EMA granted a marketing authorization under exceptional circumstances for amifampridine for the treatment of LEMS on the basis of sufficient clinical safety and efficacy data of 3,4-DAP.<sup>92</sup> After EMA approval, the annual price of 3,4-DAP rose from £730 in the UK to an estimated £29,448 leading to NICE to deny approval for amifampridine on the grounds of 1) insufficient evidence demonstrating clinical improvement in trials and 2) exponential price increase with the phosphate formulation, leaving UK patients to scramble to acquire the drug.<sup>93</sup>

Recently, a different pharmaceutical company received FDA approval for amifampridine for treatment of pediatric LEMS patients with pricing at \$80 per 10 mg pill, with anticipated yearly cost estimates of \$175,200-\$292,000 depending on dosage, leading to speculation that this medication may be used off label in adult patients.<sup>94</sup>

In summary, the US and UK approaches both led to approval of this efficacious therapy. In the US, the cost has increased 23,000% without advancement in the treatment of patients with LEMS. The availability of amifampridine through a second manufacturer may result in a less costly alternative in the US, but this remains to be seen, and even the less costly version appears unlikely to meet reasonable cost-effectiveness thresholds. In the UK, the dramatic increase in the price has led to the withdrawal of this

symptomatic treatment for LEMS patients leaving patients scrambling to find a replacement for this previously cost-effective treatment (Table 2).

### **Conclusions:**

To advance treatments for rare diseases, it is essential to continue to research and develop medications. However, in order to sustain health care systems and make treatments widely available, the approval of these medications needs to be made in a thoughtful and cost-effective manner. The US and the UK have approached the approval and coverage of medications for rare diseases in very different ways. The US exhibits a different standard for approval for rare diseases, such as requiring fewer RTCs and the use of surrogate measures as compared to approval for treatments of common diseases. This has permitted access by patients in the US to medications such as PMOs for Duchenne muscular dystrophy and edaravone for ALS. PMOs have been approved based mainly on increased dystrophin staining and not on randomized controlled trials demonstrating efficacy on patient-oriented outcomes. Similarly, edaravone has been approved after one larger negative randomized clinical trial and one smaller positive randomized clinical trial. Clinical benefits for edaravone may apply to only a small subset of patients with ALS, this may be offset by chronic infusion risks and considerable patient time commitment. In contrast to the US, the UK has asked for more data for PMOs and edaravone prior to approval. PMOs and edaravone are currently unavailable in the UK. Medications for hATTR amyloidosis and SMA are available in both the US and UK, but are approved at cost-effective prices in the UK due to the requirement to demonstrate cost-effectiveness prior to wide-spread availability. In the US, ICER can only point out that these medications are not cost-effective without the ability to rein in costs through negotiation. The primary downside to the UK approach is that these efficacious medications are available months later, but the tradeoff is more sustainable costs. Eculizumab and 3,4-DAP are examples of medications that are available in the US, but not in the UK solely because of cost. Eculizumab likely has clinical benefit for a subset of refractory MG patients. However, many effective therapies already exist for MG and it is not

cost-effective at its current price. 3,4-DAP was available in the US and UK at relatively low cost for many years, but with orphan drug status, the price increased dramatically causing the UK to no longer cover this medication, while the US has continued to allow access despite this increased cost. Overall, the UK approach has limited access to medications that do not meet traditional scientific thresholds used for common diseases and medications which do not meet cost-effective thresholds, while allowing coverage of cost-effective medications for hATTR amyloidosis and SMA. By comparison, the US has approved the use of multiple neuromuscular medications with less evidence than required for common diseases and none of the medications discussed meet cost-effectiveness thresholds.

**List of Abbreviations:**

3,4-diaminopyridine (3,4-DAP)

Acetylcholine receptor (AChR)

Amyotrophic lateral sclerosis (ALS)

Canadian Agency for Drugs and Technologies in Health (CADTH)

Committee for Medicinal Products for Human Use (CHMP)

Common Drug Review (CDR)

Duchenne Muscular Dystrophy (DMD)

Food and Drug Administration Safety and Innovation Act (FDASIA)

European Medicines Agency (EMA)

European Union (EU)

Hammersmith Functional Motor Scale-Expanded (HFMSE)

Hereditary Transthyretin Amyloidosis (hATTR)

Institute of Clinical and Economic Review (ICER)

Lambert-Eaton myasthenic syndrome (LEMS)

Myasthenia Gravis Activities of Daily Living (MG-ADL)

Myasthenia Gravis (MG)

National Health Service (NHS)

National Institute for Health and Care Excellence (NICE)

Phosphorodiamidate morpholino oligomers (PMOs)

Quality-adjusted life year (QALY)

Quantitative Myasthenia Gravis (QMG) Quantitative Myasthenia Gravis (QMG)

Randomized controlled trials (RCTs)

Revised Amyotrophic Lateral Sclerosis Rating Scale (ALSFRS-R)

Spinal muscular atrophy (SMA)

Survival of motor neuron protein (SMN)

United Kingdom (UK)

US Food and Drug Administration (FDA)

United States (US)

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**Table 1. Comparison of Annual United States Drug Costs to the Threshold Cost for Cost-Effectiveness**

<b>Orphan Drug Medication</b>	<b>Annual Price to Achieve \$150,000 per QALY</b>	<b>Annual Cost (US \$) at time of FDA approval</b>
Patisiran	\$46,488	\$450,000
Inotersen	\$25,379	\$450,000
Nusinersen	\$64,800	\$375,000 ‡
Onasemnogene abeparvovec	\$899,000	\$2,100,000 §
Risdiplam	n/a	\$340,000
Deflazacort	\$31,700	\$89,000
Eteplirsen	*	\$300,000 ¶
Golodirsen	*	\$300,000 ¶
Edaravone	\$4,350 †	\$145,000
Eculizumab	n/a	\$500,000
Amifampridine	n/a	\$375,000

Abbreviations: US \$, United States dollars; QALY, Quality-adjusted life year; FDA, United States Food and Drug Administration.

\* Value-Based Price Benchmark unable to be calculated in the absence of evidence demonstrating clinical benefits.

† Calculated based on CADTH Common Drug Review. Pharmacoeconomic Review Report: Edaravone

‡ First year cost: \$750,000

§ One-time cost

¶ Price will vary by patient weight

**Table 2. Neuromuscular Orphan Drug Therapies**

Orphan Drug Medication	Regulatory Approval		Cost-effective		Available	
	US	UK	US	UK	US	UK
Patisiran	Yes	Yes	No <sup>24</sup>	Yes <sup>29</sup>	Yes	Yes
Inotersen	Yes	Yes	No <sup>24</sup>	Yes <sup>30</sup>	Yes	Yes
Nusinersen	Yes	Yes	No <sup>42</sup>	Yes <sup>46</sup>	Yes	Yes
Onasemnogene abeparvovec	Yes	Yes	No <sup>42</sup>	pending	Yes	pending
Risdiplam	Yes	No	No	n/a	Yes	No
Deflazacort	Yes	No	No <sup>63</sup>	n/a	Yes	No
Eteplirsen	Yes	No	No <sup>63</sup>	n/a	Yes	No
Golodirsen	Yes	No	No <sup>63</sup>	n/a	Yes	No
Edaravone	Yes	No	No <sup>72</sup>	n/a	Yes	No
Eculizumab	Yes	No	No <sup>81</sup>	n/a	Yes	No
Amifampridine	Yes	No	No	n/a	Yes	No

Abbreviations: US, United States; UK, United Kingdom

Figure 1 Legend: Divergent pathways from data submission to initial approval and availability of novel treatments.