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The 10th Oligonucleotide Therapy Approved: Golodirsen for Duchenne Muscular Dystrophy

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On December 12, 2019, the Food and Drug Administration (FDA) granted accelerated approval to Sarepta Therapeutics for golodirsen to treat Duchenne muscular dystrophy (DMD) patients with eligible mutations (www.drugs.com/newdrugs/fda-approves-vyondys-53-golodirsen-duchenne-muscular-dystrophy-dmd-patients-amenable-skipping-exon-5119.html). This brings the number of FDA and/or European Medicines Agency (EMA) approved oligonucleotide drugs to 10 and the number of oligonucleotide drugs for treatment of DMD to 2 (Table 1). The approval is less controversial than that of previously approved eteplirsen, but it was still not a smooth ride.

The idea to use splice modulating as a therapy for DMD stems from the fact that lack of functional dystrophin causes severe progressive muscle wasting, while mutations that allow the production of partially functional dystrophins are associated with a less progressive disease, Becker muscular dystrophy (BMD). Antisense oligonucleotide-mediated splicing modulation for DMD aims to modulate splicing such that DMD patients can produce BMD-like dystrophin. As not all DMD patients carry the same mutation, this approach is mutation specific. However, most mutations cluster in a hotspot region and as such the skipping of certain exons applies to larger groups of patients, for example, exon 51 skipping would apply to 14% of patients, whereas exon 45 and exon 53 skipping would apply to an additional 9% and 8% of DMD patients [1,2].

Golodirsen (exon 53 skipping) and eteplirsen (exon 51 skipping) are both developed by Sarepta Therapeutics and are both phosphorodiamidate morpholino oligomers. Eteplirsen received accelerated approval in 2016 from the FDA based on increased expression in dystrophin in treated patients.

As already mentioned, this approval was controversial, and the issues involved have been discussed in detail previously [3]. In brief, according to FDA, functional benefits from treatment had at that time not been convincingly shown by Sarepta Therapeutics, whereas the increases in dystrophin in a skeletal muscle biopsy were minimal: ~0.4% after 48 weeks and ~0.9% after 188 weeks of treatment [3]. Notably, dystrophin quantification is very challenging and Sarepta Therapeutics invested a lot of effort in making its Western blotting system acceptable to FDA [4]. Still, it is questionable how accurate one can quantify very minute increases [5]. Sarepta Therapeutics has until 2021 to show evidence to FDA that eteplirsen treatment and the related minor increases in dystrophin expression slow down disease progression in a placebo-controlled trial. Thus far, functional effects such as slower decline in ambulatory and respiratory function have been presented, but these all use historic controls from natural history studies [6,7].

For golodirsen, approval was again only based on increases in dystrophin expression. Once again, no clinical benefit was shown. Golodirsen was tested in a two-stage clinical trial, where eight patients received weekly intravenous infusion with increasing doses up to 30 mg/kg golodirsen, while four patients received a placebo. Then these 12 patients were enrolled in an open label phase where they and an additional 13 patients received weekly doses of 30 mg/kg of golodirsen.

Muscle biopsy analysis detected an increase of on average 0.9% in dystrophin after 48 weeks of treatment. This result suggests that golodirsen outperforms eteplirsen treatment, which required 188 weeks to achieve this increase. However, FDA initially did not approve golodirsen and Sarepta Therapeutics received a complete response letter in August 2019 wherein FDA outlined concerns of golodirsen treatment (www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211970Orig1s000OtherActionLtrs.pdf). The first concern involved an infection risk for treated patients related to the intravenous ports installed to facilitate weekly infusions. The second concern related to renal toxicity observed in animal models at a 10-fold higher dose than the one used in humans (www.drugs.com/nda/golodirsen_190819.html).

Sarepta Therapeutics addressed the issues and will monitor the kidney function of treated patients carefully. In addition, they will need to provide evidence to FDA that golodirsen treatment results in clinical benefit, that is, results in a slower disease progression as measured by functional outcome measures, by 2024. A double-blind placebo-controlled confirmatory trial is currently ongoing (https://clinicaltrials.gov/ct2/show/NCT02500381?term=golodirsen&cond=Duchenne+Muscular+Dystrophy&draw=2&rank=4).

With the approval of golodirsen, ~22% of DMD patients in the United States now, in theory, have access to a dystrophin-restoring drug. However, not everyone who is eligible for treatment will be treated with this drug. First, the cost of the drug will likely be in the same range as eteplirsen (several hundreds of thousands of dollars per patient per year,

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Table 1. Oligonucleotide Drugs Approved by Food and Drug Administration and EMA

Drug	*Indication*	*Mechanism*	*FDA approval?*	*EMA approval?*
Fomivirsen	CMV induced retinitis	Translation block	1998	1999
Mipomirsen	Familial hypercholestolemia	RNase H	2013	No
Eteplirsen	Duchenne muscular dystrophy	Splicing modulation	2016	No
Nusinersen	Spinal muscular atrophy type	Splicing modulation	2016	2017
Inotersen	Hereditary transthyretin-mediated amyloidosis	RNase H	2018	2018
Patisiran	Hereditary transthyretin-mediated amyloidosis	RNAi	2018	2018
Valonesorsen	Hypertriglycidemia, familial chylomicronemia syndrome, familial partial lipodystrophy	RNase H		2019
Givosiran	Acute hepatic phorphoria	RNAi	2019	
Golodirsen	Duchenne muscular dystrophy	Splicing modulation	2019	

CMV, cytomegalo virus; EMA, European Medicines Agency; FDA, Food and Drug Administration.

depending on patient weight). This may be prohibitive to some individuals, depending on insurance coverage. Second, not all eligible patients may want to be treated. The weekly intravenous infusions and related hospital visits may be too burdensome for some individuals, especially considering lack of confirmed functional evidence.

Another potential concern for patients is that this is a therapeutic approach that slows down disease progression. Treatment will not bring back muscle tissue and function that is already lost. For patients in a more advanced stage of the disease, the expected benefit may not outweigh the treatment burden.

Finally, there may be patients who do not realize they are eligible for treatment. This could be because the genetic diagnosis was never made, or because the treating neurologist is unaware of the availability of the treatment. The genetics of DMD and BMD are complex and the mutation-specific therapy options require an advanced grasp of genetics. It has been identified that there is a gap in genetic knowledge in many neurologists caring for DMD patients, leading to, for example, misinterpretation of the effect of the mutation and misdiagnosing DMD as BMD and *vice versa* or misinterpreting the eligibility of a specific mutation to exon skipping or other mutation-specific approaches [8]. The field is trying to address this, for example, through writing of educational material [9], Duchenne master classes organized by TREAT-NMD and online tools such as the DMD open access variant explorer (DOVE) that helps with the interpretation of mutations (www.dmd.nl/dove).

Although Sarepta Therapeutics now has two approved DMD oligonucleotide drugs on the market, they are not the only player in the DMD exon-skipping field. Nippon Shinyaku (NS) Pharma is developing viltolarsen [10]. Viltolarsen also is a phosphoridiamidate morpholino oligomer and targets the same region in exon 53 as golodirsen. However, viltolarsen is a 21-mer, whereas golodirsen is a 25-mer oligonucleotide. Viltolarsen has been tested in clinical trials in Japan (dose finding up to 20 mg/kg and 40 and 80 mg/kg per week intravenous infusion) and in the United States at weekly intravenous doses of 40 and 80 mg/kg. After 24 weeks of treatment, dystrophin levels increased by 5.8% in skeletal muscle biopsies (www.nippon-shinyaku.co.jp/file/download.php?file_id=1388). Notably, because viltolarsen is 20% shorter than golodirsen, at a per molecule level, the 80 mg/kg dose is more than threefold higher than a 30 mg/kg dose of golodirsen.

Although both NS Pharma and Sarepta Therapeutics use Western blotting to quantify dystrophin levels, they did not use identical protocols or reference controls. As such, one cannot directly compare the 5.8% and the 0.9% increase. Regardless, it is clear that viltolarsen increases dystrophin expression and an FDA approval would be in line with the eteplirsen and golodirsen approvals. However, as with eteplirsen and goldirsen, convincing evidence from a double-blind placebo controlled trial is lacking.

NS Pharma has completed its new drug application to FDA in October 2019 and to the Japanese regulatory authorities in September 2019 and is currently performing a placebo-controlled confirmatory trial, using weekly doses of 80 mg/kg viltolarsen (https://clinicaltrials.gov/ct2/show/NCT04060199?term=viltolarsen&cond=Duchenne+Muscular+Dystrophy&draw=2&rank=1).

It remains unclear whether the low increases in dystrophin induced by these splice-switching oligonucleotides are sufficient to slow down disease progression. What is clear is that higher levels of skipping would be more beneficial. Several efforts toward developing more efficient exon-skipping compounds are currently being undertaken, both clinically and preclinically. First, Sarepta Therapeutics is conducting a dose-finding safety clinical trial with SRP-5051, an eteplirsen with an arginine-rich peptide conjugate phosphorodiamidate morpholino oligomer (pPMO) that improves tissue uptake. In animal models, treatment with pPMO resulted in dystrophin restoration in skeletal muscle, and also in heart, an organ that is difficult to reach with unconjugated PMOs [11]. However, arginine-rich peptides are known to be toxic, primarily for the kidney [12]. The question is, which comes first, the dose at which the pPMO results in exon skipping and dystrophin restoration, or the dose at which the pPMO results in renal toxicity?

Wave therapeutics was developing suvodirsen, an exon 51 targeting oligonucleotide with a phosphorothioate backbone and a combination of ribose modifications to render the oligonucleotide RNase H resistant. Suvodirsen is a stereopure

compound. The phosphorothioate backbone is chiral, and each backbone modification can be either in the L or D orientation. As such, a 20-mer phosphorothioate oligonucleotide will be a mixture of 2^{19} different oligonucleotides from a chirality perspective. For suvodirsen the chirality for each backbone linkage was set.

Defining chirality may allow discovery of optimized compounds that are better ''fit'' for their target sequences. Although this exciting hypothesis remains relatively unexplored and unproven, stereopure compounds might improve efficiency and broadly increase the impact of oligonucleotide drugs.

Unfortunately, however, Wave recently announced suvodirsen treatment did not result in an increase in dystrophin expression in biopsies from DMD patients treated for 12 or 22 weeks. Whether this reflects a fundamental problem with the concept of developing stereopure compounds, a temporary setback in optimizing a new drug design strategy, or the inherent difficulty of the delivery for DMD remains to be seen. Consequently, clinical development of suvodirsen, as well as that of an exon 53 skipping stereopure oligonucleotide, has been abandoned (www.globenewswire.com/news-release/2019/12/16/1960830/0/en/Wave-Life-Sciences-Announces-Discontinuation-of-Suvodirsen-Development-for-Duchenne-Muscular-Dystrophy.html).

Additional oligonucleotide chemistries are being evaluated preclinically. Such compounds include a conjugated tricyclo modified oligonucleotide targeting exon 51 in development by Synthena [13] and a new exon 51 skipping oligonucleotide developed by BioMarin (https://investors.biomarin.com/download/BMRN_RDDay2019_111419_FINAL_11am.pdf). These new compounds may provide the boost in potency necessary to increase dystrophin to levels where functional effects will be more apparent.

Because of the need for the mutation-specific approaches, several compounds will be required to treat larger groups of DMD patients. In addition to exon 51 and exon 53 clinical trials, an oligonucleotide to induce exon 45 skipping, which would be applicable to 8%–9% of patients, is also evaluated in clinical trials (https://clinicaltrials.gov/ct2/show/NCT04179409?cond=casimersen&draw=2&rank=2). Combined with exon 51 and exon 53 skipping this would still only treat <30% DMD patients. To treat the majority of patients, additional oligonucleotides need to be developed, whereas the group sizes for these compounds would go down quickly to <1% of patients [2]. A dialogue with regulators to smooth the development of additional exon-skipping compounds has been initiated [14]. However, the more burning question remains whether the dystrophin levels that can be restored by the current generation of compounds are sufficient to slow down disease progression and, if so, to which extent.

Author Disclosure Statement

A.A.R. discloses being employed by LUMC that has patents on exon-skipping technology, some of which have been licensed to BioMarin and subsequently sublicensed to Sarepta Therapeutics. As coinventor of some of these patents, A.A.R. is entitled to a share of royalties. A.A.R. further discloses being *ad hoc* consultant for PTC Therapeutics, Sarepta Therapeutics, CRISPR Therapeutics, Summit PLC, Alpha Anomeric, BioMarin Pharmaceuticals, Inc., Eisai, Astra Zeneca, Santhera, Audentes, Global Guidepoint and GLG consultancy, Grunenthal, Wave, and BioClinica, having been a member of the Duchenne Network Steering Committee (BioMarin) and being a member of the scientific advisory boards of ProQR, hybridize therapeutics, silence therapeutics, Sarepta Therapeutics, and Philae Pharmaceuticals. Remuneration for these activities is paid to LUMC. LUMC also received speaker honoraria from PTC Therapeutics and BioMarin Pharmaceuticals and funding for contract research from Italpharmaco and Alpha Anomeric. D.R.C. is a consultant for Sarepta Therapeutics.

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