The US Food and Drug Administration (FDA) has twice delayed a final decision on whether it will approve new drug application (NDA) 206488 for eteplirsen injection for intravenous infusion, sponsored by Sarepta Therapeutics, Inc. (Sarepta). The agency has requested additional clinical data from the sponsor multiple times in the last year for the product, proposed as a treatment for Duchenne muscular dystrophy (DMD), a rare, degenerative neuromuscular disorder that affects primarily young boys.

DMD is characterised by progressive muscle loss and weakness and premature death from respiratory or cardiac failure before the age of 30. The disorder is caused by mutations in the dystrophin gene, resulting in the near absence of the protein dystrophin. Lacking dystrophin, muscle cells are fragile and easily damaged.

The condition is diagnosed in approximately 1 in every 3500 live male births and is the most frequent of the early-onset muscular dystrophies that occur almost exclusively in males. According to the National Institute of Neurological Disorders and Stroke (NINDS), DMD symptoms begin in the toddler years, with progressive weakness, frequent falls, and clumsiness caused by degenerating muscle fibres in the legs and pelvis. As the disease progresses, affected boys become unable to run, jump, or climb stairs. Without aggressive care, those affected by DMD die in their late teens or early 20s.

Current treatment options include corticosteroids, such as prednisone, used to slow the rate of muscle deterioration. This class of medication can cause side-effects such as weight gain, facial changes, and bone fragility. Other treatments include immunosuppressant drugs such as cyclosporine and azathioprine, which work to delay damage to dying muscle cells. Short-term relief for muscle spasms can be provided by mexiletine, baclofen, dantrolene, and quinine.

These drugs, though effective for many patients, only provide short-term treatment of symptoms. They do nothing to halt or cure the disease. That is why so much hope and passion from the DMD community of patients and caregivers has been put into support for new treatment options such as eteplirsen.
DMD is caused by the absence of functional dystrophin in affected patients’ muscle tissue. Eteplirsen is designed to target the underlying cause of DMD, by enabling the production of a functional dystrophin protein in patients with mutations amenable to exon 51 skipping. Approximately 13% of those with DMD are estimated to have a mutation targeted by exon 51 skipping.

Eteplirsen uses Sarepta’s novel phosphorodiamidate morpholino oligomer (PMO)-based chemistry and proprietary exon-skipping technology to skip exon 51 of the dystrophin gene, thereby enabling the repair of these specific genetic mutations. By skipping exon 51, eteplirsen may restore the gene’s ability to make a shorter, but still functional, form of dystrophin from messenger RNA. Promoting the synthesis of a truncated dystrophin protein is intended to stabilise or significantly slow the disease process and prolong and improve the quality of life for patients with DMD, according to the sponsor.

At the FDA’s request, Sarepta used the Western blot method to measure dystrophin production in new muscle tissue samples taken from 11 of the 12 patients treated with eteplirsen during the Phase II Study 201/202. Nine of the 11 eteplirsen-treated patients had measurable dystrophin production, assessed by independent monitors. Sarepta also conducted the same Western blot analysis on muscle tissue from nine untreated DMD patients, but only one of these samples showed measurable dystrophin.

SUBHEAD: Advisory Committee Meeting Brings Out Passionate Supporters

During an April 2016 meeting of the FDA’s Peripheral and Central Nervous System Drugs Advisory Committee (PCNSDAC), the agency asked the committee to consider whether the sponsor’s demonstrated 0.9% rise in dystrophin levels was enough of an increase to “be reasonably likely to predict clinical benefit.” The majority of committee members stated they did not think the margin was large enough.

The agency also asked the panel about the clinical meaning of the amount of dystrophin observed in the muscles of eteplirsen-treated patients, taking into consideration the range of amounts of dystrophin known to be typically present in patients with DMD and in patients with Becker muscular dystrophy. Clinical evidence of efficacy in Study 201/202 was considered weak by most committee members. Though secondary clinical endpoints seemed positive, panellists said historical controls used were flawed. Several committee members said they would have preferred a placebo-controlled trial.

Committee members concluded that there was only moderate evidence of dystrophin production, and also that it was unclear what a clinically significant amount of dystrophin would be. It was not well understood whether the manufactured dystrophin is better or worse than naturally produced dystrophin in patients, and overall, panellists agreed that the sponsor’s primary endpoint was ambiguous.

During the open public hearing portion of the PCNSDAC meeting, more than 50 advocates and patients stood before the agency and the committee to give more than 2½ hours of emotional testimony about living with DMD. They gave anecdotal evidence of success after treatment with eteplirsen, and panellists admitted to being swayed by the testimony.

The FDA had advised that anecdote and emotion do not change the data with which the agency and panel are confronted. William Dunn, MD, director of the FDA’s Division of Neurology Products, stated during the meeting that he and the agency were also deeply moved by the patients and their advocates, and the agency would take all of the testimony into consideration as it moves forward in its decision-making about eteplirsen approval.

Ultimately, many committee members stated that the final voting question, concerning whether substantial evidence of effectiveness was shown, was difficult to answer. If considering FDA standards for approval, they said, eteplirsen did not meet expectations. The pivotal study was not adequate or well-controlled.

Several panellists said they were troubled that the meaningful testimony offered by family members and patients about the positive effects of the drug on their lives was not reflected in the study data. They agreed that there is more information to learn about this drug, particularly with extension studies ongoing, and encouraged the sponsor to continue gathering relevant data.

For its part, the FDA announced in late May 2016 that additional time would be required for its review and final decision on the eteplirsen NDA, and in June 2016 asked Sarepta for additional dystrophin data from biopsies already obtained from DMD patients. The Prescription Drug User Fee Act (PDUFA) target action date for eteplirsen was May 26, 2016. The agency said it would continue to work past that date and strive to complete its work in as timely a manner as possible.

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Advancing Mobile Data Capture in Clinical Trials

The last decade has seen the emergence of a new player in the completion of clinical outcome assessments (COAs): electronic data collection. This method of capturing information directly from patients is proving to be an ever-more valuable tool for sponsors, sites and patients themselves, facilitated by the global growth of mobile technology. It has created a new, more efficient way to access patients and provides an ideal platform for capturing assessment data, commonly known as patient-reported outcomes (PRO).

At its core, mobile technology is able to support the diaries, scales and questionnaires required for capturing electronic PROs (ePROs) during trials. However, the advantage mobile ePRO holds over paper and other types of ePRO devices lies in the provision of a simple intuitive interface for patients, that facilitates the two-way communication vital in keeping patients engaged. For example, educational and motivational content can be delivered via messaging and in-app notifications throughout a patient’s participation in a clinical trial.

The barriers to the use of mobile ePRO have been broken down through the incorporation of data security measures to protect patient data, the validation of a wide range of instruments from paper entry to mobile, and the reassurance of regulatory acceptability – both through public statements such as the comment from the FDA that the “BYOD (Bring Your Own Device) approach does not contravene 21 CFR Part 11” and, perhaps more substantially, the use of mobile ePRO to collect primary outcomes data in numerous product approvals in Europe and the USA.

This shift away from ePRO device provisioning towards an approach where patients are able to use their own mobile devices has caused much debate within the healthcare industry. There has been the mistaken belief that when introducing BYOD into a protocol, enrolment of patients with a specific type of device is the only option. That approach would be offering choice in the same way that Henry Ford did to the choice of colour for his Model T car – you can bring any device to this study, as long as it’s an Android with Ice Cream version 12.2 OS – an approach which would seriously limit study eligibility criteria.

The reality of BYOD in clinical trials is very different. The provision of ePRO solutions for BYOD trials almost always introduces an element of provisioning in pre-approval studies. The key is to be able to identify the specifications of the patient’s device and ascertain whether it meets the requirements for the individual study. If not, then a suitable device can be provisioned – a flexible provisioning approach. The provisioning rate for such studies is decreasing year-on-year as the uptake of more advanced mobile technology increases: in the US almost ¾ of adults over 65 now own a mobile phone². In pre-approval studies we are seeing rates anywhere from around 50% provisioned down to as low as 10%, depending on the study population. This provides two significant benefits: not only does it enable the patient to use their own device, the one they personally selected from all available options; but it significantly reduces the cost and logistical complexity of device provisioning for sponsors.

A decade ago, no-one could have predicted just how far mobile technology would advance and how it would become such an integral part of daily life for people around the world. Mobile eCOA has now been proven to be a highly beneficial and versatile option for data capture in clinical trials. Evidence shows that this modern, more efficient method of data collection has significantly improved PROs and has been used – both through a provisioning and a BYOD approach – to collect primary outcomes data in Europe and US drug approvals.

The industry continues to escalate its adoption of mobile ePRO, which is now is expected to become the standard approach to collecting self-reported clinical data.

References
1. Panel session at MCT Congress 2014

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