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Emerging Drugs
for Duchenne
Muscular Dystrophy

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Summary

- Duchenne muscular dystrophy (DMD) is a rare and severe disorder that affects primarily young boys. It begins with progressive muscle weakness that evolves to loss of ambulation and further progresses to early morbidity and mortality.
- DMD is caused by a mutation of the dystrophin gene that results in a lack of dystrophin, a protein that is necessary for muscle cell function.
- The mainstays of current therapy to treat DMD are corticosteroids and assistive devices.
- This bulletin focuses on new and emerging drugs for DMD with completed phase IIb or phase III trials and includes ataluren (nonsense mutation suppression), eteplirsen (exon 51 skipping), and idebenone (adenosine triphosphate [ATP] modulation). Ezutromid (utrophin modulation) and givinostat (histone deacetylase inhibition) are in early stages of development.
- The evidence reviewed showed that, while these drugs increased the production of new dystrophin, they generally had limited impact on ambulation and physical function.

Background

DMD is an X-linked genetic disorder and is the most common form of muscular dystrophy in childhood, affecting one in 3,500 to 6,000 newborn males.^{1,2} There are approximately 50,000 cases of DMD worldwide.³ In 2015, it was estimated there were 794 DMD patients in Canada.⁴ The disease is caused by mutations of the DMD gene that codes for dystrophin, a protein that protects the integrity of muscle cells.⁵⁻⁷

The loss of dystrophin in patients with DMD disrupts the muscle membrane and fibres. This leads to progressive muscle weakness, gait disturbance, motor development delay, calf hypertrophy, and elevated creatine kinase levels (a biomarker reflecting muscle damage).⁶ Most affected children first present with symptoms between the ages of three and five years. These symptoms gradually worsen with time, eventually leading to loss of ambulation and the need to use a wheelchair by early adolescence.⁸ Boys with DMD may also have intellectual disability, speech delay, and cognitive impairment.^{6,8} Further progression of the disease leads to respiratory insufficiency and cardiomyopathy, which is present in almost all patients by 18 years of age.⁸ Death typically occurs before the third decade of life due to cardiorespiratory complications.^{6,8,9} Female carriers of the DMD mutation are largely asymptomatic, although 20% to 30% may present with mild-to-moderate muscle weakness, and are at increased risk for dilated cardiomyopathy.⁸

There is an unmet medical need for the treatment of DMD, as there is no cure and the standard of care is limited to corticosteroids and assistive devices.

The Technology

There are currently two genetic strategies in development that attempt to re-establish the expression of dystrophin in muscle: suppression of nonsense mutations and exon skipping. Further strategies to compensate for the lack of dystrophin include utrophin upregulation, ATP modulation, and histone deacetylase inhibition.

- Ataluren suppresses nonsense mutations, which enables the production of a modified dystrophin protein.
- Eteplirsen is a third-generation synthetic antisense oligonucleotide (AON) that is designed to induce exon 51 skipping.
- Ezutromid is an utrophin modulator that aims to replace lost dystrophin with utrophin.
- Givinostat is a histone deacetylase inhibitor that may help to rebalance the repair process in muscle by increasing muscle regeneration.
- Idebenone is an ATP production modulator that helps dystrophic muscle cells maintain their cellular energy supply and protects cells from oxidative stress.

Appendix 1 contains further details on their mechanisms of action.

Regulatory Status

On July 31, 2014, the European Commission granted a marketing authorization for ataluren (Translarna; PTC Therapeutics) that is valid throughout the European Union. It is also approved in

Iceland, Liechtenstein, Norway, Israel, and South Korea. It is indicated for the treatment of DMD in ambulatory patients five years and older with nonsense mutations.¹⁰ In Canada, the manufacturer, PTC Therapeutics, had initially submitted the dossier to Health Canada for review in August 2015; in March 2016, it chose to cancel the submission in order to re-file at a later date with additional data.¹¹

The US FDA approved eteplirsen (AVI 4658, Exondys 51; Sarepta Therapeutics) on September 19, 2016 through the accelerated approval pathway, with the condition that a confirmatory clinical trial be conducted.¹² In the US, it is indicated for patients who have confirmed mutation of the dystrophin gene amenable to exon 51 skipping, which is about 13% of the DMD population.¹³

Ezutromid (SMT C1100; Summit Therapeutics), givinostat (ITF2357; Italfarmaco SpA), and idebenone (CV 2619, Raxone or Catena; Santhera Pharmaceuticals) have not received regulatory approval in any country for the treatment of DMD.

Target Population

Ataluren's intended use is in patients with confirmed nonsense mutation in the dystrophin gene, representing 10% to 15% of the DMD population.^{14,15}

Eteplirsen is for use in children with confirmed mutation of the DMD gene amenable to exon 51 skipping, which is approximately 13% of the DMD population.¹⁶

Idebenone has been studied in DMD patients with declining lung function.^{17,18}

Ezutromid and givinostat have the potential to be used in all DMD patients.^{19,20}

Current Practice

There is currently no cure for DMD. Multidisciplinary management includes assistive devices, rehabilitative management, treatment of complications, and genetic counselling.⁸ Recent advances in management, as well as pharmacological treatment with corticosteroids, has resulted in survival and quality-of-life improvements.^{8,21}

- The mainstay of treatment for DMD is glucocorticoids. There is evidence of their benefit in improving lung and motor function, stabilizing muscle strength, reducing the risk of scoliosis, and prolonging ambulation.^{1,6,22} The dosage for oral prednisone is generally 0.75mg/kg daily, although alternate-day and high weekend-dose regimens are also used.²² Deflazacort, a derivative of prednisone, is also used in DMD patients at 0.9 mg/kg/day, although it is available only through the Special Access Programme in Canada.
- Cardiac disease, including left ventricular dysfunction and heart failure, is usually managed with angiotensin-converting enzyme inhibitors and beta blockers.²³
- Various methods of non-invasive mechanical ventilation have played a major role in increasing survival in DMD patients from their late teens to their late 20s.¹⁸
- Orthopedic interventions and physical therapy are also necessary to reduce contractures, manage scoliosis, and maintain independence.⁸

Summary of the Evidence

Methods

A literature search was conducted using the following bibliographic databases: MEDLINE, PubMed, Embase, and the Cochrane Library (2016, Issue 11). Grey literature was identified by searching relevant sections of the *Grey Matters* checklist (<https://www.cadth.ca/grey-matters>). Methodological filters were applied to limit retrieval to randomized controlled trials (RCTs). The search was limited to English-language documents published between Jan. 1, 2011 and Dec. 1, 2016. Regular alerts were established to update the search until March 6, 2017. Conference abstracts published between Jan. 1, 2014 and Dec. 1, 2016 were included in the search results.

Efficacy

Appendix 2 contains the characteristics and results of the included trials. Information on ongoing phase III trials for DMD medications is available in Appendix 3.

Study Design

A total of four RCTs are included as evidence: one phase IIb trial and one phase III trial on ataluren; one phase IIb trial on eteplirsen; and one phase III trial on idebenone. Information on

an open-label extension trial on eteplirsen is also included. No published phase IIb or phase III trial information on givinostat or ezutromid was found.

Population

The ataluren and eteplirsen trials enrolled patients between the ages of five and 14 years who were ambulatory at screening; the majority were on corticosteroids. The idebenone study population ranged in age from 10 to 18 years, was largely non-ambulatory, and was not on corticosteroids.

Interventions

Ataluren: In the phase IIb trial on ataluren (n = 174), 57 patients were randomized to placebo, 57 patients were randomized to ataluren 40 mg/kg/day in three divided doses, and 60 patients were randomized to ataluren 80 mg/kg/day in three divided doses for 48 weeks.¹⁴ The phase III RCT (n = 230) compared ataluren 40 mg/kg day, given in three divided doses (n = 115), with placebo (n = 115) for 48 weeks.¹⁵

Eteplirsen: In Study 201, four patients were randomized to the placebo group, four patients to 30 mg/kg of eteplirsen weekly, and four patients to 50 mg/kg of eteplirsen weekly for 24 weeks.¹⁶ Study 202 is an extension trial of Study 201 in which eteplirsen-treated patients continued treatment at the same dose and placebo patients were assigned either dose of the study medication starting at week 25 (called the placebo-delayed group; it was unclear if the assignment was randomized). Study 202 is 212 weeks in duration and is ongoing.¹⁶

Idebenone: A total of 66 patients were enrolled in the phase III trial: 32 patients were randomized to idebenone 900 mg orally, given as 300 mg three times daily; 32 patients were randomized to matching placebo; and one patient was allocated to the same treatment as his brother. Study duration was 52 weeks.¹⁷

Outcomes Measured in Trials

Ambulation

The outcome measures for trials involving drugs aimed at prolonging ambulation in patients with DMD included the six-minute walk test (6MWT; measured in the ataluren and eteplirsen trials); the North Star Ambulatory Assessment (NSAA; measured in the ataluren phase III trial), and physical functioning (measured in both ataluren trials).

- The 6MWT assesses physical function and endurance by measuring the distance a person is able to walk during a total of six minutes on a hard, flat surface. The primary measurement of the 6MWT is the six-minute walk distance (6MWD). A 30 metre change in distance on the 6MWT has been proposed as the minimal clinically important difference in DMD patients with nonsense mutations.²⁴
- The NSAA, is a functional scale consisting of 17 activities to measure disease progression in ambulatory DMD patients.²⁵ For each of these activities, the NSAA assigns a grade from 0 (unable to achieve activity independently) to 2 ("normal" – able to achieve activity without modification), with a maximum possible score of 34, which may be linearized from 0 to 100.²⁵
- Other aspects of physical functioning were measured as a change in time-function tests in two trials evaluating ataluren. The tests included four-stair ascent, four-stair descent, 10-metre walk or run, and supine to stand.^{14,15}

Dystrophin Production

The eteplirsen trial measured the change in dystrophin production by performing muscle biopsies to measure dystrophin-positive fibres. The laboratory tests used to quantify dystrophin were immunohistochemical and immunofluorescence analyses, and Western Blot.¹⁶

Pulmonary Function

Change in respiratory function was measured as peak expiratory flow as percentage predicted (PEF%p). Patients self-assessed their respiratory function weekly.¹⁷

Results

A summary of the results is available in Table 1.

Ambulation

Ataluren: In Study 007, the difference in the mean change from baseline in the 6MWD was 29.7 metres for ataluren 40 mg/kg compared with placebo ($P = 0.149$). There was no statistically significant difference between ataluren 80 mg/kg and placebo. For ataluren 40 mg/kg compared with placebo, the difference in the mean change from baseline in timed function tests showed an improvement of 2.4 seconds in time to climb stairs (95% confidence interval [CI], -4.8 to 0), an improvement of 1.6 seconds in time to descend four stairs (95% CI, 4.2 to 1.0), and an improvement of 1.4 seconds in time to run or walk 10 metres

(95% CI, -3.7 to 0.9).¹⁴ In Study 020, there was a difference of 15.4 metres in the mean change from baseline in 6MWD between ataluren 40 mg/kg and placebo (statistical significance not reported).¹⁵ There was no statistically significant difference in NSAA mean score between ataluren 40 mg/kg and placebo ($P = 0.268$).²⁵

Eteplirsen: At 24 weeks, the 30 mg/kg group and the placebo group had worsening ambulation, as measured by the 6MWT, compared with baseline (-128.2 metres and -25.8 metres, respectively); there was no change for the patients who were administered 50 mg/kg of eteplirsen. At 48 weeks, the ambulation of the group receiving 50 mg/kg of eteplirsen improved by 21 metres; whereas with 30 mg/kg of eteplirsen, there was a decline of 153.4 metres on the 6MWT from baseline.¹⁶

Dystrophin Production

Eteplirsen: At 24 weeks, the production of dystrophin increased by 22.9% from baseline in patients who were administered 30 mg/kg of eteplirsen. Compared with placebo, this increase was statistically significant (mean difference 27%, $P < 0.002$).¹⁶ In the open-label extension trial, at 48 weeks, the production of dystrophin increased by 51.7% from baseline in the patients who were administered 30 mg/kg of eteplirsen.¹⁶

Pulmonary Function

Idebenone: In the DELOS trial, both the treated group and the placebo group had worsening respiratory function at week 52. The placebo group had a decline in PEF%_p of 8.84% compared with a decline of 2.57% in the idebenone-treated group, resulting in a difference of 6.27% (95% CI, 0.61 to 11.93; $P = 0.031$).

Study Limitations

The eteplirsen trial (Study 201) had 12 participants, thereby limiting its power and generalizability.

The production of new dystrophin as a surrogate biomarker has been used to grant conditional approval of eteplirsen in the US.³¹ However, the amount of new functional dystrophin required to produce a clinically meaningful outcome has yet to be quantified.³² In some rare cases, the absence of dystrophin does not cause severe disease, as would be predicted.³³

There are also questions regarding the reliability and consistency of the current methods used to quantify dystrophin production.^{33,34} Different samples using different techniques can yield varying results that cannot be compared, as they have been

tested at different times, with different methods, and at different testing sites. For example, the average dystrophin protein level after 180 weeks of treatment with eteplirsen was increased by only 0.93% ± 84% when tested by Western Blot in Study 202.^{31,33}

All RCTs were double-blinded and placebo-controlled. However, one important limitation is the duration of the trials. In studies of less than 52 weeks, the 6MWT is more likely to detect changes in patients who are in a rapid decline phase of the disease.¹⁵ The production of dystrophin may take months, but demonstrating a positive clinical outcome such as a delay to a non-ambulatory state and improved life expectancy may take years to demonstrate.³⁴

Safety

Eteplirsen

In the group that received treatment ($n = 8$), the US prescribing information indicates that the most frequent adverse events reported in Study 201 ($n = 12$) were balance disorder (38%; $n = 3$), vomiting (25%; $n = 2$), and contact dermatitis (25%; $n = 2$). No adverse events were reported in the placebo group (0%; $n = 0$).³¹

The US monograph further states that in combined clinical studies of patients who received eteplirsen 30 mg/kg ($n = 88$) for up to 208 weeks, adverse events that reached a frequency $\geq 10\%$ included vomiting, contusion, excoriation, arthralgia, rash, catheter-site pain, and upper respiratory tract infection.³¹

Transient infusion-related reactions such as erythema, facial flushing, and elevated temperature have also been reported.³¹

Ataluren

Frequent adverse events reported in Study 007 were vomiting (ataluren 40 mg/kg: 56.1%; placebo: 38.6%), diarrhea (ataluren 40 mg/kg: 19.3%; placebo: 24.6%), nausea (ataluren 40 mg/kg: 14.0%; placebo: 12.3%), and upper abdominal pain (ataluren 40 mg/kg: 15.8%; placebo: 15.8%). Serious adverse events in Study 007 were reported in 3.5% of the ataluren 40 mg/kg arm and 5.3% in the placebo arm. None of the participants withdrew from the study due to treatment-related adverse events.²⁶ Exposure to ataluren may cause elevation of liver enzymes, serum lipids, and serum creatinine; these effects were reversible upon discontinuation.³⁵ Concomitant administration with aminoglycosides is contraindicated.^{15,26}

Table 1: Results of Phase IIb and Phase III Clinical Trials

Study	Results
Ataluren	
<p>Bushby, 2014^{14,26} Study 007</p>	<p>At week 48</p> <p>Mean change from baseline in 6MWT:</p> <ul style="list-style-type: none"> • placebo = -42.6 m • ataluren 40 mg/kg = -12.9 m • ataluren 80 mg/kg = -44.8 m <p>Difference in the mean change from baseline in 6MWT:</p> <ul style="list-style-type: none"> • ataluren 40 mg/kg vs. placebo = 29.7 m; <i>P</i> = 0.149 • ataluren 80 mg/kg vs. placebo = -0.7 m; <i>P</i> = NS <p>Difference in the mean change from baseline in timed function tests:</p> <ul style="list-style-type: none"> • ataluren 40 mg/kg vs. placebo (95% CI) <ul style="list-style-type: none"> ◦ time to climb 4 stairs = -2.4 s (-4.8 to 0) ◦ time to descend 4 stairs = -1.6 s (-4.2 to 1.0) ◦ run/walk 10 m = -1.4 s (-3.7 to 0.9) ◦ supine to stand = -0.0 s (-2.5 to 2.4) • ataluren 80 mg/kg vs. placebo (95% CI) <ul style="list-style-type: none"> ◦ time to climb 4 stairs = -1.3 s (-4.0 to 1.4) ◦ time to descend 4 stairs = -1.1 s (-3.9 to 1.7) ◦ run/walk 10 m = -0.7s (-3.0 to 1.7) ◦ supine to stand = -0.2 s (-2.6 to 2.2)
<p>McDonald, 2017^{15,25,27,28} Study 020 ACT DMD</p>	<p>At week 48</p> <p>Difference in the mean change from baseline in 6MWD:</p> <ul style="list-style-type: none"> • ataluren 40 mg/day vs. placebo = 15.4 m (<i>P</i> = NR) <p>Difference in the mean change from baseline in timed function tests:</p> <ul style="list-style-type: none"> • ataluren 40 mg/day vs. placebo: <ul style="list-style-type: none"> ◦ time to climb 4 stairs = -1.4 s (<i>P</i> = 0.058) ◦ time to descend 4 stairs = -2.0 s (<i>P</i> = 0.012) ◦ run/walk 10 m: -1.1 s (<i>P</i> = 0.117) <p>NSAA-observed mean score:</p> <ul style="list-style-type: none"> • ataluren 40 mg/day = -7.0 • placebo = -8.5 <p>Difference in NSAA-observed mean score:</p> <ul style="list-style-type: none"> • ataluren 40 mg/day vs. placebo = 1.5 (<i>P</i> = 0.268)

Study	Results
Eteplirsen	
Mendel, 2013^{16,29} Study 201	<p>At 24 weeks</p> <p>Mean absolute change from baseline in the percentage of dystrophin-positive fibres (SE):</p> <ul style="list-style-type: none"> • placebo = -4.0% (2.92) • eteplirsen 30 mg/kg = 22.9% (2.90) • eteplirsen 50 mg/kg = not measured <p>Difference in the mean change from baseline of percentage of dystrophin-positive fibres:</p> <ul style="list-style-type: none"> • eteplirsen 30 mg/kg vs. placebo = 27%; <i>P</i> < 0.002 <p>Mean change from baseline in 6MWT (SD):</p> <ul style="list-style-type: none"> • placebo = -25.8 m (30.6) • eteplirsen 30 mg/kg = -128.2 m (36.6) • eteplirsen 50 mg/kg = -0.3 m (31.2)
Mendel, 2016^{16,30} Study 202	<p>At 48 weeks</p> <p>Mean absolute change from baseline in the percentage of dystrophin-positive fibres (SE):</p> <ul style="list-style-type: none"> • combined eteplirsen 30 mg/kg and 50 mg/kg = 47.3% (3.89) • eteplirsen 30 mg/kg = 51.7% (3.54) • eteplirsen 50 mg/kg = 42.9 (6.72) • placebo-delayed eteplirsen 30 mg/kg = 33.6% (5.23) • placebo-delayed eteplirsen 50 mg/kg = 41.8% (13.3) <p>Mean change from baseline in 6MWT (SD)</p> <ul style="list-style-type: none"> • eteplirsen 30 mg/kg = -153.4 m (38.7) • eteplirsen 50 mg/kg = 21 m (38.2) • placebo-delayed eteplirsen (both doses combined) = -68.4 m (37.6)
Idebenone	
Buyse, 2015^{17,18} DELOS	<p>At week 52</p> <p>Change in PEF%p from baseline:</p> <ul style="list-style-type: none"> • idebenone = -2.57% (95% CI: -6.68 to 1.54) • placebo = -8.84% (95% CI: -12.73 to -4.95) <p>Mean % difference:</p> <ul style="list-style-type: none"> • idebenone vs. placebo = 6.27% (95% CI: 0.61 to 11.93); <i>P</i> = 0.031

6MWD = six-minute walking distance; 6MWT = six-minute walk test; CI = confidence interval; m = metre; NR = not reported; NS = not significant; NSAA = North Star Ambulatory Assessment; PEF%p = peak expiratory flow as percentage predicted; s = second; SD = standard deviation; SE = standard error; vs. = versus.

Note: Statistical significance reported when available.

Idebenone

No deaths were reported in the DELOS trial.¹⁷ Serious adverse events were reported in 6% of idebenone-treated patients and in 15% of placebo patients. Withdrawals due to adverse events were reported in two idebenone patients (due to sleep apnea syndrome in one patient and diarrhea in another patient) and in one placebo patient (due to supraventricular arrhythmia and respiratory failure with pneumonia). The most frequently reported adverse events included nasopharyngitis (26%) and headache (20%), which were balanced across treatment groups. Diarrhea was more commonly reported in the idebenone group compared with placebo (25% versus 12%, respectively).¹⁷

Post-market reports of reduced blood cell counts and increased liver function have been reported (in the indication for Friedreich's ataxia).³⁶

Administration and Cost

Eteplirsen

In the US, eteplirsen is available in 100 mg/2 mL and 500 mg/10 mL single-dose vials. The recommended dose is 30 mg/kg administered once weekly as a 35-minute to 60-minute intravenous infusion.³¹ The cost of eteplirsen is estimated to be approximately US\$300,000 per year.³⁷

Ataluren

In Europe, ataluren is available in sachets containing oral granules for suspension in strengths of 125 mg, 250 mg, and 1,000 mg. The granules can be taken orally after mixing with either a liquid or semi-solid food such as yogurt. The recommended dosage of 40 mg/kg/day is to be divided into three doses (10 mg/kg in the morning, 10 mg/kg at midday, and 20 mg/kg in the evening).³⁸

The projected benchmark cost in Canada is \$264 for a 250 mg sachet and \$1,056 for the 1,000 mg sachet.³⁹ Assuming a weight of 25 kg, the cost per year would be \$385,440.

Idebenone

Idebenone is administered as two 150 mg film-coated tablets that are given orally three times a day (900 mg/day) with meals.⁴⁰ The cost of idebenone has yet to be determined.

Concurrent Developments

AONs targeting exon 51 are the most advanced exon-skipping therapy in clinical development; other similar therapies designed to skip mutations on other exons (44, 45, 53, 56) are in the initial stages of clinical trials.^{7,41,42}

The use of adeno-associated virus (AAV) vectors to deliver working copies of the DMD gene to muscles is being investigated; however, early clinical results have been unremarkable and this type of therapy presents some challenges, such as immune reactions to the newly translated protein.^{3,7}

An emerging tool of bacterial origin for correcting mutations is gene editing with clustered regularly interspaced short palindromic repeats. This method has been successfully paired with AAV vectors to treat dystrophic mice with positive initial results.⁴³

CAT-1004, an orally administered small molecule targeted to inhibit activated NF-kappaB, a major inflammatory and muscle degeneration factor implicated in DMD pathophysiology, is being investigated in phase I and phase II studies.⁴⁴

Vamorolone, an anti-inflammatory and potential alternative to prednisone, is being investigated in phase II trials with the hope that it may have the beneficial effects of prednisone with reduced side effects.^{45,46}

Lastly, inhibition of myostatin, which is a negative inhibitor of muscle mass, is a novel strategy in regenerating muscle in muscular dystrophy patients. ACE-031, a fusion protein designed to bind and disrupt the activity of myostatin, was investigated and showed a trend for improvements in the 6MWT; however, the study was stopped due to adverse events of epistaxis and telangiectasias.⁴⁷ Other trials investigating different myostatin inhibitors, such as follistatin and PF-06252616 (phase II), are being conducted.^{6,48}

Implementation Issues

Current access to DMD drugs is limited, as patients in Canada are generally restricted to participation in clinical trials. Patient organizations such as TREAT-NMD and Muscular Dystrophy Canada may help eligible patients participate in trials, although many studies are recruiting by invitation only.⁶

Once these medications receive regulatory approval, a major barrier to the uptake of novel therapies for DMD is likely to be cost. Furthermore, there is the possibility for some of the medications to be used in combination, which will increase the cost further. Criteria will need to be determined to establish which patients are more likely to benefit, and to identify when a drug is no longer beneficial.

Administering medication to children can be challenging. Idefenone and ataluren are orally administered and require multiple daily administrations. The oral route of administration may not be ideal in DMD patients who have trouble swallowing, although ataluren has the advantage of being available as granules for suspension. Eteplirsen needs to be infused intravenously once weekly, which could become a barrier, depending on accessibility and availability of treatment centres.

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Appendix 1: Mechanism of Action

The Duchenne muscular dystrophy (DMD) gene is expressed mainly in skeletal and cardiac muscle and is the largest known human gene.⁴⁹ It contains 79 exons and is subject to complex and numerous mutations due to its large size. While the majority of DMD cases are maternally inherited, one-third result from spontaneous mutations that vary in severity.^{6,7}

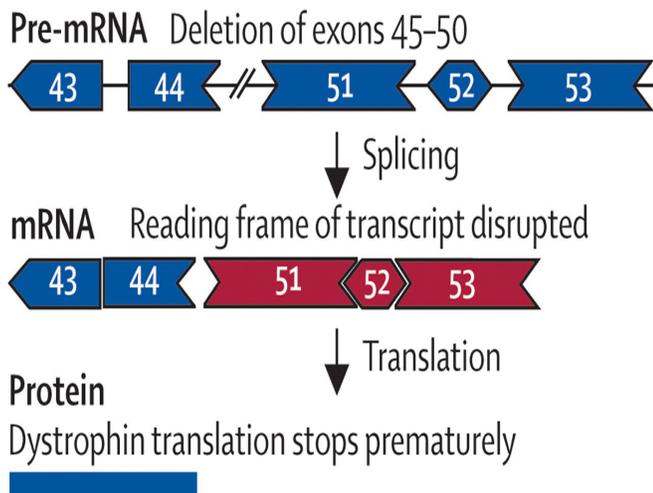
The majority of DMD mutations are large mutations that involve one or more exons. Approximately 86% of these are deletions, and 14% are duplications.^{5,7} The remainder are small mutations, including insertions, nonsense mutations that cause premature cessation of the protein formation, and splicing mutations.^{6,7,49}

Exon Skipping

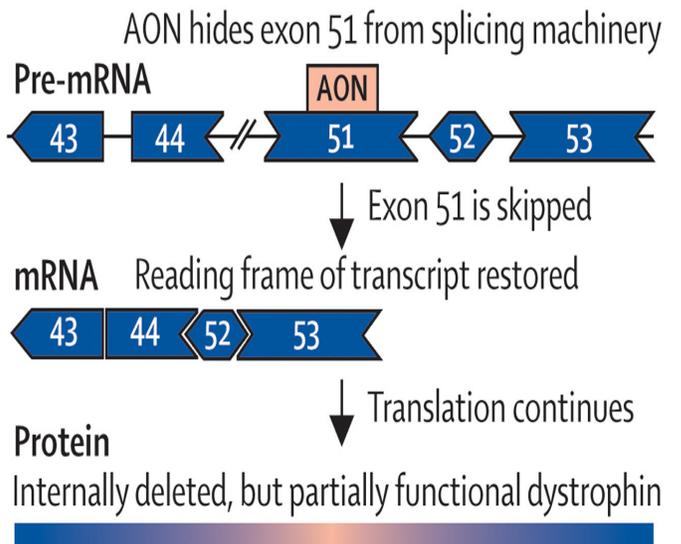
The method of exon skipping utilizes antisense oligonucleotides (AONs) sequences to skip the exons with mutations, with the aim of correcting specific gene mutations.^{49,50} This results in partial production of a truncated dystrophin protein and, consequently, partially preserves dystrophin function.⁵⁰⁻⁵² Exon skipping works in cases of deletions, but is less amenable to correcting duplications because the AONs cannot differentiate between the original and duplicated exons.⁷ The most frequent mutations on the DMD gene occur between exons 45 and 55, and therapy aimed at skipping exon 51 has been of particular interest, as it accounts for 13% of DMD mutations.¹⁶ Figure 1 depicts the use of an AON to target a specific exon and restore the reading frame in order to enable the production of a partially truncated dystrophin.

Figure 1: Exon Skipping by Antisense Oligonucleotides to Restore Reading Frame

Duchenne muscular dystrophy



Exon skipping to reframe transcripts



AON = antisense oligonucleotide; mRNA= messenger ribonucleic acid.

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Eteplirsen is a third-generation synthetic AON that is designed to induce exon 51 skipping. There are several other exon-skipping therapies in clinical trials that target different exons: exon 44 (PRO044); exon 45 (DS-5141b, PRO045, SRP4045); and exon 53 (SRP4053, PRO053, NS-065/NCNP-01).^{6,7}

Of note, drisapersen (Kyndrisa by Biomarin Pharmaceutical), a second-generation AON that induces exon 51 skipping, was rejected by the FDA in January 2016 after it concluded that a standard of evidence of effectiveness had not been met.¹² On May 31, 2016, BioMarin announced that it was discontinuing clinical and regulatory developments of Kyndrisa, as well as three other products: BMN 044, BMN 045, and BMN 053, which were in phase II studies for DMD.³⁷

Stop-Codon Read-Through Nonsense Suppression Therapy

This treatment is applicable to approximately 10% to 15% of males with DMD who have a point mutation involving a premature stop codon.^{1,49} This particular mutation causes the translation of the dystrophin protein to be stopped prematurely, and ultimately produces a shortened and dysfunctional dystrophin protein.

Ataluren was developed to target these mutations by enabling read-through of the premature stop codon and enabling translation and production of a modified dystrophin protein.^{6,49,53} The resulting increase in dystrophin production would be expected to stabilize or slow disease progression. Ataluren's mechanism selects only premature stop codons; it does not interfere with normal stop codons.¹⁵

Utrophin Upregulation

Utrophin has structural and protein-binding properties similar to dystrophin and shares 80% of its sequence.^{1,49,54} It is produced during the early stages of muscle-fibre development and is switched off in maturing muscle fibres, at which point dystrophin is produced. When muscle fibre is damaged, utrophin expression is switched on again and production is increased to re-establish the continuity of myotubes and promote the repair mechanism.

Ezutromid is an utrophin modulator that aims to replace lost dystrophin with utrophin.⁵⁴ Utrophin modulators have the advantage of being potentially applicable to all DMD patients, irrespective of the underlying genetic defect.⁵⁵ Ezutromid is at the phase IIa development stage.

Adenosine Triphosphate Modulation

Idebenone is a short-chain benzoquinone that increases the energy output of cell mitochondria. It carries and drops off electrons within the mitochondria numerous times, thereby providing additional electrons to the mitochondria. It is also an antioxidant and can neutralize destructive free radicals in cells. All of these activities help dystrophic muscle cells maintain their cellular energy supply, and they protect the cells from oxidative stress.⁵⁶

Idebenone is an adenosine triphosphate production modulator and is aimed at DMD patients when they become non-ambulatory and their respiratory function begins to significantly decline (ages 10 to 18).⁴⁰ It is currently being tested in DMD patients for slowing the loss of pulmonary function (Appendix 2).

Histone Deacetylase Inhibitor Activity

Histone deacetylase inhibitor activity is upregulated in dystrophic muscles and contributes to the impairment of muscle regeneration. Givinostat is a histone deacetylase inhibitor currently being studied for the treatment of DMD (Appendix 2). Givinostat promotes the transcription of a number of factors that are important in muscle regeneration, such as follistatin. The expected effects are an increase in muscle mass and the prevention of muscle degeneration. Givinostat also has potent anti-inflammatory effects; these activities may help to rebalance the repair process in muscle with increased muscle regeneration and reduced fatty infiltration and fibrosis.⁵⁷

A phase I single-arm trial showed that givinostat did not improve outcomes such as the six-minute walk test and NSAA.²⁰ A phase III trial is being planned (Appendix 2).

Appendix 2: Characteristics and Results of Phase IIb and Phase III Clinical Trials

Author, Year Name of Study Country	Study Design Study Duration	Population	Intervention Comparator	Results
Eteplirsen				
Mendel, 2013 ^{16,29} Study 201 US	Phase IIb, RCT, DB 24 weeks	N = 12 Boys aged 7–13 y with confirmed out of frame DMD deletions potentially amenable to exon 51 skipping Able to walk 200 m to 400 m on 6MWT On stable glucocorticoids for ≥ 24 weeks	<i>Intervention:</i> Eteplirsen 30 mg/kg infused over 60 minutes once a week (n = 4) Eteplirsen 50 mg/kg infused over 60 minutes once a week (n = 4) <i>Comparator:</i> Placebo of phosphate-buffered saline solution infused over 60 minutes once a week (n = 4)	At 24 weeks Mean absolute change from baseline in the percentage of dystrophin-positive fibres (SE): • placebo = -4.0% (2.92) • eteplirsen 30 mg/kg = 22.9% (2.90) • eteplirsen 50 mg/kg = not measured Difference in the mean change from baseline of percentage of dystrophin-positive fibres: • eteplirsen 30 mg/kg vs. placebo = 27%, <i>P</i> < 0.002 Mean change from baseline in 6MWT (SD): • placebo = -25.8 m (30.6) • eteplirsen 30 mg/kg = -128.2 m (36.6) • eteplirsen 50 mg/kg = -0.3 m (31.2)
Mendel, 2016 ^{16,30} Study 202 US	OL Extension trial of Study 201 (ongoing)	As per Study 201	<i>Intervention:</i> As per Study 201; placebo-treated patients switched to eteplirsen 30 mg/kg (n = 2) or 50 mg/kg (n = 2)	At 48 weeks Mean absolute change from baseline in the percentage of dystrophin-positive fibres (SE): • combined eteplirsen 30 mg/kg and 50 mg/kg = 47.3% (3.89) • eteplirsen 30 mg/kg = 51.7% (3.54) • eteplirsen 50 mg/kg = 42.9 (6.72) • placebo-delayed eteplirsen 30 mg/kg = 33.6% (5.23) • placebo-delayed eteplirsen 50 mg/kg = 41.8% (13.3) Mean change from baseline in 6MWT (SD) • eteplirsen 30 mg/kg = -153.4 m (38.7) • eteplirsen 50 mg/kg = 21 m (38.2) • placebo-delayed eteplirsen (both doses combined) = -68.4 m (37.6)

Author, Year Name of Study Country	Study Design Study Duration	Population	Intervention Comparator	Results
Ataluren				
Bushby, 2014 ^{14,26} Study 007 Multi-centre	Phase IIb RCT, DB 48 weeks	N = 174 Males ≥ 5 years of age with documented nonsense mutation Median age: 8 y Onset of symptoms before age 9, all had elevated CK, able to walk ≥ 75 m unassisted 71% were on stable corticosteroid therapy	<i>Intervention:</i> Ataluren 40 mg/kg/day in 3 divided doses (10, 10, 20 mg/kg) (n = 57) Ataluren 80 mg/kg/day in 3 divided doses (20 mg, 20 mg, 40 mg/kg) (n = 60) <i>Comparator:</i> Placebo t.i.d. (n = 57)	At week 48 Mean change from baseline in 6MWT: • placebo = -42.6 m • ataluren 40 mg/kg = -12.9 m • ataluren 80 mg/kg = -44.8 m Difference in the mean change from baseline in 6MWT: • ataluren 40 mg/kg vs. placebo = 29.7 m, <i>P</i> = 0.149 • ataluren 80 mg/kg vs. placebo = -0.7 m, <i>P</i> = NS Difference in the mean change from baseline in timed function tests: • ataluren 40 mg/kg vs. placebo (95% CI) ◦ time to climb 4 stairs = -2.4 s (-4.8 to 0) ◦ time to descend 4 stairs = -1.6 s (-4.2 to 1.0) ◦ run/walk 10 m = -1.4 s (-3.7 to 0.9) ◦ supine to stand = -0.0 s (-2.5 to 2.4) • ataluren 80 mg/kg vs. placebo (95% CI): ◦ time to climb 4 stairs = -1.3 s (-4.0 to 1.4) ◦ time to descend 4 stairs = -1.1 s (-3.9 to 1.7) ◦ run/walk 10 m = -0.7s (-3.0 to 1.7) ◦ supine to stand = -0.2 s (-2.6 to 2.2)

Author, Year Name of Study Country	Study Design Study Duration	Population	Intervention Comparator	Results
McDonald, 2017 <small>15,25,27,28</small> Study 020 ACT DMD Multi-centre	Phase III RCT, DB 48 weeks	N = 230 Males aged 7–14 y with genetically confirmed nonsense mutation On corticosteroids for ≥ 6 months and no changes to therapy for at least 3 months prior to enrolment 6MWT ≥ 150 m and ≤ 80% of predicted age and height	<i>Intervention:</i> Ataluren 40 mg/day in divided doses t.i.d. (n = 115) <i>Comparator:</i> placebo t.i.d. (n = 115)	At week 48 Difference in the mean change from baseline in 6MWD: • ataluren 40 mg/day vs. placebo = 15.4 m (<i>P</i> = NR) Difference in the mean change from baseline in timed function tests: • ataluren 40 mg/day vs. placebo: ◦ time to climb 4 stairs = -1.4 second (<i>P</i> = 0.058) ◦ time to descend 4 stairs = -2.0 second (<i>P</i> = 0.012) ◦ run/walk 10 m: -1.1 second (<i>P</i> = 0.117) NSAA-observed mean score: • ataluren 40 mg/day = -7.0 • placebo = -8.5 Difference in NSAA-observed mean score: • ataluren 40 mg/day vs. placebo = 1.5 (<i>P</i> = 0.268)
Idebenone				
Buyse, 2015^{17,18} DELOS Multi-centre	Phase III RCT, DB 52 weeks	N = 65 (+ 1 non-randomized patient) Mean age: 14.3 (range 10–18) y Not on glucocorticoids (stopped 12 months prior to entry) PEF% _p ≤ 80% at baseline. 92% were non-ambulatory	<i>Intervention:</i> Idebenone 900 mg/day (two 150 mg film-coated tablets t.i.d.) (n = 32) <i>Comparator:</i> matching placebo (n = 34)	At week 52 Change in PEF% _p from baseline: • idebenone = -2.57% (95% CI, -6.68 to 1.54) • placebo = -8.84% (95% CI, -12.73 to -4.95) Mean % difference: • idebenone vs. placebo = 6.27% (95% CI, 0.61 to 11.93), <i>P</i> = 0.031

6MWD = six-minute walking distance; 6MWT = six-minute walk test; CI = confidence interval; CK = creatine kinase; DB = double-blind; DMD = Duchenne muscular dystrophy; m = metre, NR = not reported; NS = not significant; NSAA = North Star Ambulatory Assessment; OL = open-label; PEF%_p = peak expiratory flow as percentage predicted; RCT = randomized controlled trial; s = second; SE = standard error; t.i.d. = three time daily; vs. = versus; y = years.

Note: Statistical significance reported when available.

Appendix 3: Ongoing Phase III Clinical Trials for Duchenne Muscular Dystrophy

Drug Study Phase Sample Size	Purpose of Study	Study Design/Intervention/ Comparator/Duration	Outcomes Measured	Stage of Trial
Eteplirsien⁵⁸ Confirmatory Study(PROMOVI) (NCT02255552) Phase III N = 160 (estimated)	To provide confirmatory evidence of eteplirsien in patients with DMD amenable to skipping exon 51 On stable dose of corticosteroids for at least 24 weeks	<i>Design:</i> Open-label, multi-centre, non-randomized <i>Intervention:</i> eteplirsien 30 mg/kg as an intravenous infusion once a week in boys with genetic deletions amenable to exon 51 skipping <i>Comparator:</i> Untreated group (will not receive eteplirsien) in boys with DMD who do not have exon 51 mutation <i>Duration:</i> 96 weeks	<i>Primary:</i> Change in 6MWT distance from baseline <i>Secondary:</i> Percentage of dystrophin-positive fibres; maximum inspiratory/ expiratory pressure as % predicted	Currently recruiting participants Estimated completion: May 2019
Idebenone⁵⁹ Evaluating Idebenone in Patients With Duchenne Muscular Dystrophy (DMD) Taking Glucocorticoid Steroids (SIDEROS) [NCT02814019] Phase III N = 266 (estimated)	To assess the efficacy of idebenone in delaying the loss of respiratory function in patients with DMD receiving concomitant glucocorticoid steroids	<i>Design:</i> Double-blind, randomized, placebo-controlled <i>Intervention:</i> Idebenone 900 mg/day (in three divided daily doses) <i>Comparator:</i> Placebo <i>Duration:</i> 78 weeks	<i>Primary:</i> Change from baseline in FVC%p at week 78 <i>Secondary:</i> Change from baseline in forced vital capacity and inspiratory flow reserve at week 78	Currently recruiting participants Estimated completion: August 2019
Givinostat⁶⁰ Efficacy and Safety of Givinostat in Ambulant Patients With DMD (NCT02851797) Phase III N = 213 (estimated)	To assess efficacy and safety of givinostat in ambulant patients with DMD who were 6 to 17 years old	<i>Design:</i> Randomized, double-blind, parallel group, placebo-controlled <i>Intervention:</i> Givinostat 10 mg/mL (dose not specified) twice daily <i>Comparator:</i> Placebo <i>Duration:</i> 18 months	<i>Primary:</i> Mean change in time to climb 4 stairs <i>Secondary:</i> 6MWT, time to rise from floor, measure change in muscle mass	Not yet open for participant recruitment Estimated completion: June 2020

6MWT = six-minute walk test; DMD = Duchenne muscular dystrophy; FVC%p = forced vital capacity per cent predicted.