Idebenone Delays Respiratory Decline in Duchenne Muscular Dystrophy

Written by Nicola Parry

Gunnar Buyse, MD, PhD, University of Leuven, Leuven, Belgium, presented data from a phase 3, double-blind, randomized, placebo-controlled study [DELOS; Buyse GM et al. *Lancet*. 2015] of the efficacy, safety, and tolerability of idebenone in patients aged 10 to 18 years with Duchenne muscular dystrophy (DMD). The results demonstrated that idebenone significantly reduced the decline of respiratory function in patients with DMD who were not receiving corticosteroids.

DMD is a devastating condition with no cure, and it is the most common type of muscular degenerative disease worldwide. Progressive respiratory failure is a major cause of morbidity in patients, and it is often the main cause of death in young adulthood.

According to Prof Buyse, in patients with DMD, dystrophin deficiency causes a calcium ion influx into muscle cells, resulting in mitochondrial dysfunction with reduced cellular energy production and increased formation of reactive oxygen species. Idebenone represents a novel treatment approach for DMD, he explained. It is a synthetic quinone compound that stimulates electron transfer and cellular energy production, and functions as an antioxidant, thereby counteracting some of the biochemical changes that occur in DMD.

Based on successful preclinical [Buyse GM et al. *Eur Heart J*. 2009] and phase 2 [Buyse GM et al. *Pediatr Pulmonol*. 2013; Buyse GM et al. *Neuromusc Disord*. 2011] data, Prof Buyse and colleagues therefore conducted a multicenter, international, randomized controlled phase 3 trial (DELOS) to assess the efficacy and safety of idebenone in DMD.

The study randomized and treated 64 patients aged between 10 and 18 years who were not currently receiving chronic corticosteroid treatment, of whom 92% were confined to wheelchairs.

Patients received either idebenone 900 mg/day (n = 31) or placebo (n = 33) for 52 weeks. The primary end point was peak expiratory flow (a measure of respiratory strength) as a percentage of predicted normal (PEF%p). Secondary end points included forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1).

At 52 weeks, idebenone significantly reduced the decline in PEF%p compared with placebo in the modified intention-to-treat (ITT) population (–3.05 vs –9.01; $P = .04$; Figure 1) and the ITT population (–2.57 vs –8.84; $P = .03$), representing a reduction in loss of PEF%p of 66% and 71%, respectively.

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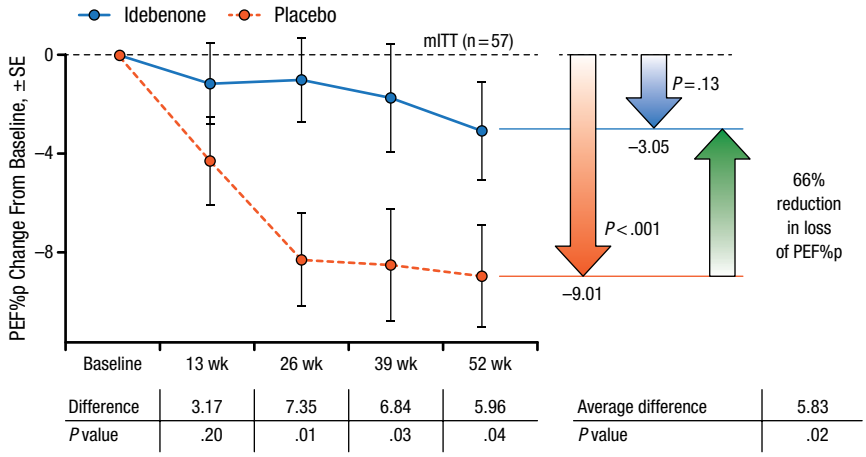
Figure 1. Effect of Idebenone on Peak Expiratory Flow in mITT Population



Difference	3.17	7.35	6.84	5.96	Average difference	5.83
P value	.20	.01	.03	.04	*P* value	.02

mITT, modified intention-to-treat; PEF%p, peak expiratory flow as a percentage of predicted normal.
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Idebenone also resulted in a 37% reduction in loss of FVC as a percentage of predicted normal, although not significantly (–5.67 vs –8.95; $P = .08$), and a 78% reduction in loss of FEV_1 as a percentage of predicted normal (–2.40 vs –10.68; $P = .03$) in the ITT population.

This study represents the first successful phase 3 trial in DMD, and it demonstrates significant benefit of idebenone treatment in patients with this disease. Treatment with idebenone was also safe and well tolerated, concluded Prof Buyse.

TARGET: Nasal Delivery of Sumatriptan Powder Improves Functioning in Patients With Migraine

Written by Maria Vinall

Data presented by Peter J. McAllister, MD, New England Institute for Neurology and Headache, Stamford, Connecticut, USA, indicate that, in addition to providing migraine relief, breath-powered nasal delivery of low-dose sumatriptan powder (AVP-825) is associated with significantly improved functioning and a reduction in disability.

AVP-825 is an investigational drug-device combination product containing sumatriptan powder (22 mg) delivered intranasally via breath-powered technology. Clinical trials of AVP-825 in the acute treatment of migraine have shown headache relief at levels comparable with the most effective triptans [Cady RK et al. *Headache.* 2015; Djupesland PG et al. *Cephalalgia.* 2010]. Dr McAllister presented secondary outcomes from a recent phase 3 study [Cady RK et al. *Headache.* 2015] showing that AVP-825 shortens the time to meaningful relief and lowers clinical disability scores compared with placebo.

TARGET [NCT01462812] was a phase 3, multicenter, parallel-group trial composed of men and women diagnosed with episodic migraine ≥1 year prior to screening who reported 1 to 8 migraines per month during the 12 months prior to prescreening, had verified airflow through both nostrils, had the ability to close the soft palate, and demonstrated ability to use the breath-powered device. Participants were randomized to AVP-825 (n = 108) or a placebo (n = 104). Migraine symptoms were recorded predose and at 10, 15, 30, 45, 60, 90, and 120 minutes postdose. The Headache Impact Test (HIT-6) and clinical disability scale scores were used to measure headache-associated burden and disability at baseline.

Participants (mean age 42 years; 83.5% women; 85.8% white) reported a mean of 4.5 headaches per month; most (83%) associated with moderate pain and without aura (81.1%). HIT-6 results showed substantial headache burden and associated disability, ie, approximately 39% of patients routinely experience impairment with work and 34% with daily activities; 50% always or very often experience severe pain; and 80% always or very often wish they could lie down. At baseline, 57% of patients randomized to AVP-825 and 55% of placebo patients had clinical disability scale scores indicating moderate or severe disability.

The median time to meaningful headache relief with AVP-825 was 47.5 minutes. Compared with the placebo group, significantly more patients using AVP-825 reported experiencing meaningful relief by 120 minutes ($P = .0004$). Clinical disability scale scores improved over time; by 45 minutes postdose, these scores were significantly reduced in the AVP-825 group ($P = .0343$).

Disability was significantly reduced at 120 minutes postdose in the AVP-825 group compared with the placebo group ($P = .0430$). Specifically, by the 120-minute end point, 19% of patients treated with AVP-825 and 35% of placebo-treated patients reported moderate or severe disability compared with 57% and 55%, respectively, at baseline ($P < .05$).

MR CLEAN: Endovascular Therapy Improves Outcomes in Acute Ischemic Stroke

Written by Nicola Parry

Diederik Dippel, MD, PhD, Erasmus University Medical Center, Rotterdam, the Netherlands, presented updated data from MR CLEAN, a multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke (AIS) in the Netherlands [ISRCTN10888758]. The results demonstrated improved functional outcomes in patients who received endovascular therapy up to 6 hours after stroke onset in the proximal anterior circulation, in addition to best medical care [Berkhemer OA et al. *N Engl J Med.* 2015].

According to Prof Dippel, more than one-third of patients with AIS have a proximal intracranial arterial occlusion. Intravenous (IV) administration of tissue plasminogen activator (tPA) within 4.5 hours of stroke onset clears the blockage in only about one-third of these and leads to recovery in only 10%.

Although previous trials showed no effect of intra-arterial treatment on functional outcomes in AIS, a new study was needed, he stressed, owing to improved patient selection from widespread use of computed tomography, rapid access to treatment in the Netherlands, and new endovascular treatment modalities. Prof Dippel and colleagues therefore conducted MR CLEAN to evaluate the