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

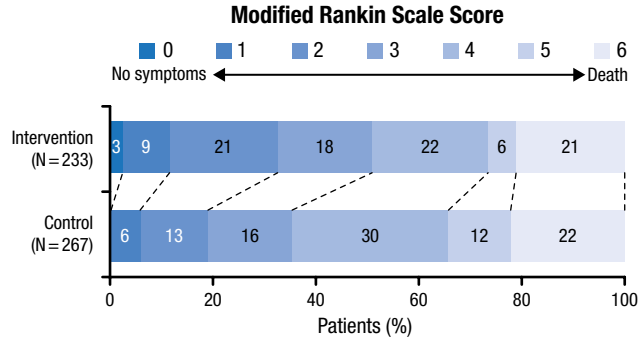
Written by Nicola Parry

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

Figure 1. Effect of Endovascular Intervention on Functional Outcome at 90 Days



From *N Engl J Med*, Berkhemer OA et al., A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke, Volume No. 372, 11-20. Copyright © (2015) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

effect of intra-arterial treatment on functional outcome in AIS, on a background of best medical management.

The open-label trial [Berkhemer OA et al. *N Engl J Med*. 2015] included 500 patients (≥ 18 years) with AIS with cranial arterial anterior circulation occlusion that was confirmed on imaging and could be treated intra-arterially within 6 hours of symptom onset. NIH Stroke Scale (NIHSS) scores were ≥ 2. The primary outcome was the score on the modified Rankin Scale (mRS) at 90 days.

Participants received usual care (which could include IV alteplase) and were randomized to also receive either intra-arterial intervention (n = 233) or no additional treatment (n = 267). The time from onset to groin puncture in the intervention group was 260 minutes.

Patients in the intervention group had lower mRS categories, consistent with improved function, at 90 days (adjusted OR, 1.67; 95% CI, 1.21 to 2.30; Figure 1).

Prof Dippel also highlighted unpublished subanalyses from MR CLEAN. Intra-arterial intervention was superior to no additional treatment for all age groups in the study, in particular, for those aged ≥ 80 years (adjusted OR, 3.24; 95% CI, 1.22 to 8.62), and for those with the most severe strokes (NIHSS score ≥ 20; adjusted OR, 1.85; 95% CI, 1.06 to 2.31).

Compared with controls, intra-arterial intervention with local anesthesia (adjusted OR, 2.79; 95% CI, 1.70 to 4.59) was more likely to result in a good outcome than general anesthesia (adjusted OR, 1.09; 95% CI, 0.56 to 2.12), which showed no benefit over usual care.

Prof Dippel concluded that intra-arterial intervention on a background of usual best stroke care is effective and safe in many patients if provided within 6 hours of stroke onset.

AVP-825 Produces Effective, Well-Tolerated Migraine Relief

Written by Maria Vinall

High-dose (100 mg) sumatriptan tablets are commonly used to treat migraines; however, they have a relatively slow onset of action and may be poorly absorbed because of impaired gastrointestinal impairment occurring during migraine. This has led to the development of a low-dose (22 mg) sumatriptan powder delivered intranasally through a breath-powered delivery system (AVP-825). In a pharmacokinetic study, AVP-825 was shown to have fewer triptan-associated adverse events and have a faster onset of action compared with tablets [Obaidi M et al. *Headache*. 2013]. Results of pooled analysis of data from a phase 2 [Djupesland PG et al. *Cephalalgia*. 2010] and a phase 3 [TARGET; Cady RK et al. *Headache*. 2015] trial of AVP-825 were presented in a poster by Roger K. Cady, MD, Headache Care Center, Springfield, Missouri, USA, and showed that AVP-825 conferred rapid headache relief that was sustained over placebo out to 48 hours and was well tolerated.

Both studies were randomized, multicenter, double-blind, placebo-controlled, parallel-group trials that included patients with migraines, with headache severity scores of grade 2 or 3 for at least 1 year, and with no known resistance to sumatriptan. The objective was to evaluate the efficacy and safety of AVP-825 using a larger, uniform pool of patients. Outcomes included:

1. the proportion of patients with pain relief, freedom from pain, no clinical disability, and no migraine-associated symptoms (eg, nausea, vomiting, photophobia, and phonophobia); and
2. meaningful relief (subject-reported interpretation) within 120 minutes of treatment.

The percentage of patients requiring rescue medication over the first 48 hours after treatment, and the frequency and severity of treatment-emergent adverse events (TEAEs), were also recorded.

The pooled study included 279 patients randomized to either AVP-825 (n = 143) or placebo (n = 136). Significantly more patients receiving AVP-825 experienced pain relief (defined as reduction of their headache severity score from moderate or severe to mild or none) 30 to 120 minutes after treatment compared with those receiving placebo ($P < .01$; Figure 1).

Similarly, a higher percentage of patients experienced relief from pain (defined as reduction of their headache severity score from mild, moderate, or severe to none) than those receiving placebo, significantly ($P < .05$) at 60, 90, and 120 minutes post-administration (Figure 2).