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Jagged1 as a modifier of the DMD phenotype: What is next?

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Absence of functional dystrophin causes muscle degeneration in Duchenne muscular dystrophy (DMD), but additional factors involved in the pathogenesis remain poorly understood and represent an unexplored territory for therapy. Among the different animal models for DMD, the most similar to the human condition is the golden retriever muscular dystrophy (GRMD) dog. We identified two milder affected GRMD dogs (escapers), despite the absence of muscle dystrophin, utrophin upregulation and elevated serum creatine kinase (CK) levels. To understand what is behind their escaper phenotype we used three independent genomic approaches Genome association analysis (GWA) which allowed to identify a chromosomal region associated with the escaper phenotype. Only one gene within this region, *Jagged1* showed altered mRNA expression when comparing muscle tissue from escaper and severely affected dogs. By whole genome sequencing analysis of the candidate region we found a variant present only in escaper GRMD dogs that creates a *myogenin* binding site in the *Jagged1* promoter, which leads to its increased expression. Overexpression of *jagged1* also rescued the dystrophic phenotype in the dystrophin-deficient *sapj*e zebrafish model. Interestingly, in a recent study from another group, *Jagged1* was reported to be downregulated in serum from DMD boys when compared to normal samples. These findings support the hypothesis according to which the milder phenotype in the escaper GRMD dogs is associated to *Jagged1* overexpression. More recently we observed in an "in vitro" assay that *Jagged1* overexpression, identified in mesenchymal stromal cells secretome from a normal donor, decreased apoptosis when in contact with myoblasts from a DMD patient. Understanding the molecular mechanism behind the beneficial effect of *Jagged1* overexpression in dystrophic muscle can lead to new targets for therapy.

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Vision DMD: Vamorolone drug development program for Duchenne muscular dystrophy

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Vamorolone (VBP15) is a first-in-human dissociative steroid that has shown improved safety and efficacy in mouse models of Duchenne muscular dystrophy compared to corticosteroids. Here, we present phase 1 data in healthy volunteers, and study designs for testing of safety and efficacy in DMD boys (phase 2a, US sites; phase 2b pivotal studies EU/Israel/Australian sites). Vamorolone PK data show strong adherence to dose linearity and dose proportionality, with relatively little subject–subject variation (both SAD and MAD). The PK for the MAD cohorts was very similar to the SAD cohorts, showing little if any drug accumulation, consistent with the short half-life and daily dosing schedule. For the food effect group, a high fat meal was given to a cohort of phase I SAD volunteers with the 8.0 mg/kg dose of vamorolone. These data were then compared to the fasted 8.0 mg/kg cohort data. The comparison showed that absorption was increased by 2.5-fold by the high fat meal, consistent with the lipophilic character of vamorolone. There were no adverse events precluding further escalations in dosing. The anticipated therapeutic dose is estimated between 1.0–8.0 mg/kg/day, and this is the dose range proposed in the later phase II first-in-patient studies. One subject in the 20 mg/kg/day cohort showed mild elevations of liver enzymes, and drug dosing was halted. No drug-treated subjects in the 1.0, 3.0 or 9.0 mg/kg/day showed elevations of liver enzymes. Safety pharmacodynamics biomarker studies showed that vamorolone had an improved safety window for adrenal suppression (100-fold increase in therapeutic window), and no evidence of insulin resistance or immune suppression, compared to prednisone studies reported in the literature. The phase studies in DMD boys use an innovative design, including extensive use of serum biomarkers (both safety and efficacy), and novel clinical outcome measures (time to stand, change in BMI).

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Idebenone reduces respiratory complications in patients with Duchenne muscular dystrophy

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In Duchenne muscular dystrophy (DMD), progressive loss of respiratory function leads to restrictive pulmonary disease and places patients at significant risk for severe respiratory complications. Of particular concern are ineffective cough, secretion retention and recurrent respiratory tract infections. In a Phase 3 randomized controlled trial in DMD patients 10–18 years of age and not taking concomitant glucocorticoids (GCs) (DELOS trial; Buyse *et al*, Lancet 2015), idebenone at 900 mg/day reduced the loss of respiratory function over a 1-year study period. In a post-hoc analysis of DELOS, "bronchopulmonary adverse events" (BAEs) were defined by a study-independent physician. More patients in the placebo group than in the idebenone group reported BAEs (placebo: 17 of 33 patients, 28 events; idebenone: 6 of 31 patients, 7 events). The Hazard ratios (HR) calculated "by patient" (HR 0.33, $p = 0.0187$) and for "all BAEs" (HR 0.28, $p = 0.0026$) indicated a clear idebenone treatment effect. The overall duration of BAEs was 222 days (placebo) vs. 82 days (idebenone). In addition, there was also a difference in the use of systemic antibiotics typically utilized for the treatment of BAEs. In the placebo group, 13 patients (39.4%) reported 17 episodes of antibiotic use compared to 7 patients (22.6%) reporting 8 episodes of antibiotic use in the idebenone group. Furthermore, patients in the placebo group used systemic antibiotics for longer (105 days) compared to patients in the idebenone group (65 days). In conclusion, this post-hoc analysis of DELOS indicates that the protective effect of idebenone on respiratory function is associated with a reduced risk of bronchopulmonary adverse events and a reduced need for systemic antibiotics.

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Treatment effect of idebenone on inspiratory function in patients with Duchenne muscular dystrophy

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Assessment of dynamic inspiratory function may provide valuable information about the degree and progression of pulmonary function decline in patients with DMD. The aims of this study were to characterize inspiratory function and to assess the efficacy of idebenone on this pulmonary function outcome in a large and well-characterized cohort of 10–18 year old DMD patients not taking glucocorticosteroids enrolled in the randomized controlled DELOS trial (Buyse et al., Lancet 2015). We evaluated the treatment effect on the highest flow generated during an inspiratory FVC maneuver (maximum inspiratory flow; V'I,max(FVC)), the ratio between the largest inspiratory flow during tidal breathing (tidal inspiratory flow; V'I,max(t)) and the V'I,max(FVC), and the Inspiratory Flow Reserve (IFR; fraction of the maximum flow not used during tidal breathing). DMD patients in both treatment groups (idebenone, N = 31; placebo: N = 33) had comparable and abnormally low V'I,max(FVC) at baseline. During the study period, V'I, max(FVC) further declined by −0.29 L/s in patients on placebo (95% CI: −0.51, −0.08; p = 0.008 at week 52), whereas it remained stable in patients on idebenone (change from baseline to week 52: 0.01 L/s; 95% CI: −0.22, 0.24; p = 0.950). The between-group difference favoring idebenone was 0.27 L/s (p = 0.043) at week 26 and 0.30 L/s (p = 0.061) at week 52. In addition, during the study period, the IFR improved by 2.8% in patients receiving idebenone and worsened by −3.0% among patients on placebo (between-group difference 5.8% at week 52; p = 0.040). This study further characterizes dynamic inspiratory dysfunction in DMD, and indicates that idebenone preserved dynamic inspiratory muscle function in patients with DMD.

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A phase III double-blind, randomized, placebo-controlled study (SIDEROS) assessing the efficacy of idebenone in slowing the rate of respiratory function loss in patients with Duchenne muscular dystrophy receiving glucocorticoid steroids

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In DMD, progressive weakness of respiratory muscles leads to restrictive respiratory disease, hypoventilation, ineffective cough, recurrent pulmonary infections, and eventually respiratory failure. In a Phase 3 randomized, placebo-controlled trial (DELOS trial; Buyse et al., Lancet 2015) in DMD patients 10–18 years of age not taking concomitant glucocorticoid steroids (GCs), idebenone significantly slowed the rate of decline in respiratory function over the 1-year study period. In an earlier Phase 2 randomized placebo-controlled pilot trial (DELPHI; Buyse et al., 2011) in DMD patients 8–16 years of age, idebenone slowed the rate of decline in respiratory function in GC non-using patients, while GC-using patients were predominantly not in the decline phase of their respiratory disease. SIDEROS is a multi-center trial of the efficacy of idebenone in slowing the rate of respiratory function decline in 266 GC-using DMD patients in the respiratory decline phase of their disease (30% ≤ Forced Vital Capacity percent predicted (FVC%p) ≤ 80%). The study will be conducted in the U.S. and Europe and patients will be randomized in a 1:1 ratio to 900 mg/day idebenone (two 150 mg tablets to be taken three times a day with meals) or to matching placebo for a duration of 78 weeks. Patients must be able to provide reliable and reproducible FVC assessments and must have been on a stable GC regimen for at least 12 months prior to Baseline. The primary endpoint is the change from Baseline to Week 78 in FVC%p assessed using hospital-based spirometry. Secondary endpoints include other measures of expiratory and inspiratory functions assessed using hospital-based spirometry as well as a portable hand-held device designed for regular use at home.

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CAT-1004, an oral agent targeting NF-kB: MoveDMD trial results in Duchenne muscular dystrophy (DMD)

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In DMD, muscle NF-kB is activated from infancy, driving inflammation, muscle degeneration and inhibiting muscle regeneration. CAT-1004 is an oral small molecule that inhibits NF-kB and improves muscle degeneration, regeneration, function and exercise endurance in preclinical models. In phase 1 trials in adults, CAT-1004 was generally well tolerated without safety signals and evidence of NF-kB inhibition was seen after single and multiple doses. Since T2 MRI in DMD demonstrates progressive leg muscle inflammation that is reduced with steroid therapy, a proof-of-concept study of CAT-1004 with MRI endpoints was designed. The MoveDMD trial is evaluating CAT-1004 in boys aged 4–7 with confirmed DMD who are not on glucocorticoid therapy for >6 months. Part A evaluated safety, tolerability and pharmacokinetics for 7 days at 33, 67 and 100 mg/kg/day (N = 17), with exploratory measures of NF-kB. CAT-1004 was generally well tolerated, with no serious adverse events and no drug discontinuations. The most common adverse events were gastrointestinal, primarily diarrhea (4/17); the majority of adverse events were mild. AUC and Cmax were approximately dose-proportional, and levels were consistent with those previously measured in adults, at which inhibition of NF-kB was seen. Whole blood NF-kB target gene expression was assessed by mRNA sequencing. Compared with baseline, NF-kB gene-set was significantly inhibited with the two higher doses. These results support Part B of the trial, a 12-week, double-blind, placebo-controlled efficacy trial in approximately 30 boys aged 4–7 with confirmed DMD. Endpoints will include MRI of leg muscles and the 10 meter-walk run, 4-stair-climb and time-to-stand as well as North Star Ambulatory Assessment and muscle strength. By reducing inflammation and muscle degeneration with potentially positive longer-term effects on muscle regeneration and function, CAT-1004 has the potential to be disease-modifying in DMD patients regardless of mutation type.

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RNA profiling discloses a link between circadian genes and muscle damage in Duchenne muscular dystrophy

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The muscular dystrophies are inherited genetic conditions that cause progressive weakness and loss of muscle mass. Mutations occurring in structural proteins such as dystrophin, cause muscle fibers' changes in