dose that could be administered. Halo Therapeutics has developed HT-100, a delayed-release formulation, allowing for delivery of potentially larger doses with enhanced tolerability. This new formulation has undergone initial testing in animals (canines) where it was well tolerated and resulted in similar systemic exposure to the original formulation. While these results are encouraging, the tolerability and pharmacokinetics (PK) profile of the new formulation needs to be confirmed in the DMD patient population.

The current trial is designed to provide initial safety, tolerability, and PK data in DMD participants with a broad spectrum of the disease in order to provide information regarding safety and tolerability and to inform dose selection for a future larger study to be conducted in a more homogenous DMD population. After completion of the Phase Ib ascending dose phase of this study, participants will be eligible to enroll in a 6-month, open-label extension study.

Background and supporting data on HT-100 will be presented as well as the Phase Ib and extension study clinical protocols.

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P.11.15
Recombinant human insulin-like growth factor-I (IGF-I) therapy in Duchenne Muscular Dystrophy (DMD): A 6-month prospective randomized controlled trial

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Glucocorticoids (GC) delay motor decline in DMD, but cause significant endocrine adverse effects. IGF-I offers potential as a therapeutic agent; it may improve or preserve muscle function and counter GC effects of growth failure and insulin resistance.

To determine if IGF-I therapy (1) improves or preserves muscle function and (2) improves linear growth in DMD.

Prospective randomized controlled trial of IGF-I therapy in pre-pubertal, ambulatory, GC-treated DMD boys (n = 17) compared to controls (GC alone, n = 21). IGF-I 160 mcg/kg was given daily subcutaneously for 6 months. Primary motor outcome was 6-min walk distance (6MWD), and endocrine outcomes were height velocity and change in height SD score (HtSDS). Other outcomes included changes in timed motor tests, cardiopulmonary function, insulin sensitivity and safety.

The difference of 6MWD between control and IGF-I groups at 6 months was 8.5 ± 7.0 m (mean ± SEM, p > 0.5). There were no significant differences between groups for changes in cardiopulmonary and other motor functional outcomes. Height velocity in IGF-I treated subjects was double that of controls at 6 months (6.5 ± 0.4 vs. 3.3 ± 0.3 cm/yr, p < 0.0001). HtSDS increased in treated subjects over 6 months, while declining in controls (+0.12 ± 0.03 vs. -0.13 ± 0.02, both p < 0.001). The annualized difference in AHtSDS was 0.50 ± 0.07 in treated over control subjects (p < 0.0001). Fasting glucose remained normal, but fasting insulin and HOMA-IR decreased (by 4.4 ± 2.0 mU/L and 0.9 ± 0.4 units respectively, both p < 0.05) in treated vs. control subjects. Significant treatment-related adverse events were transient intracranial hypertension (n = 1) and asymptomatic papilledema (n = 1).

In this first study of IGF-I therapy in DMD boys, 6 months of daily IGF-I significantly increased height velocity and HtSDS compared to controls, but there was no difference in motor functional outcomes.

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P.11.16
Three-dimensional gait analysis of Duchenne muscular dystrophy: A trial to evaluate the therapeutic effect of RNA/ENA chimera antisense oligonucleotide that induces dystrophin exon 45 skipping

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Duchenne muscular dystrophy (DMD) is caused by mutations in the dystrophin gene. Antisense oligonucleotide (AO)-mediated exon skipping therapy has been proposed for the treatment of DMD, producing in-frame mRNA from the out-of-frame mRNA by inducing exon exon skipping. Generally, the 6-min walk test has been used for evaluating the response to newly developed therapies, whereas it is difficult to measure the fine change. In this study three-dimensional gait analysis was used for measuring the therapeutic effect of AO85, which is an 18-mer antisense RNA/2-O, 4-C ethylene-bridged nucleic acid (ENA) chimera inducing the exon 45 skipping, in DMD case. An 8-year-old DMD case with exon 44 deletion was enrolled and received a 0.5 mg/kg IV infusion of AO85, which was administered at 1-week interval for 4 weeks. In addition to the conventional tests, his kinematic and kinetic data were collected with a 10-camera MAC3D motion analysis system (Motion Analysis Corp., Santa Rosa, CA) synchronized with an embedded Kistler force plate (Kistler Instruments Corp., Amherst, NY). This system monitors the three dimensional coordinates of the markers which were placed over the anatomical landmarks. The gait parameters were extracted using nMotion musculoskeletal (nac Image Technology Inc, Tokyo, Japan). The walking distances for 6 min before and after treatment were not apparently changed (360 m and 385 m, respectively). On the other hand, three-dimensional gait analysis revealed the decreased joint torques at knee and ankle. Furthermore, the motion of his center of mass in the vertical direction during gait was reduced. These results indicate that the treatment with AO85 improved his walking motion. Three-dimensional gait analysis could find the fine change of motor function that was not able to be detected by the conventional 6-min walk test, and is the promising method to evaluate the efficacy of exon skipping therapy.

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P.11.17
Optimization of preclinical antisense oligonucleotide development for Duchenne muscular dystrophy


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In recent years, the field of antisense oligonucleotides (AONs) as RNA modulating therapeutics has made significant progress. Several antisense drug candidates are in (pre-) clinical development for Duchenne muscular dystrophy (DMD). Their length may vary between 15 and 40 nucleotides depending on chosen chemistry, and their mechanism of action is based on highly sequence-specific binding to a target exon such that splicing regulatory factors and/or structures are interfered with. The resulting exon skipping aims to correct the transcript’s open reading frame, which is disrupted by a mutation (in 70% of cases a deletion of one or more exons) in the DMD gene of DMD patients. This approach is mutation-dependent and, although applicable to subpopulations of DMD patients with grouped mutations in the area of the targeted exon, the development of multiple AONs will be needed to treat a majority of patients. In our pre-clinical programs, selection of AON candidates depends on multiple characteristics, including pharmacology, pharmacokinetics, physico-chemical properties, and safety effects both in vitro and in vivo. Through this extensive preclinical screening we have identified the safest and most efficient
AONs in the clinical development of DMD exons 45, 52, 53, or 55, which are currently in clinical development. We have also explored further optimization of the 2′-O-methyl phosphorothioate RNA oligochemistry to improve binding affinity and stability, activity, safety, and/or synthesis procedures. For instance, the effect of chemical base modifications has been tested. Here, we present an overview of results from our extensive preclinical AON candidate selection program, and from our studies on AONs with 5-substituted pyrimidines.

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P.11.18

Design of a confirmatory phase 3, multicenter, randomized, double-blind, placebo-controlled study of ataluren in patients with nonsense mutation Duchenne muscular dystrophy

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Duchenne muscular dystrophy (DMD) is a rare, X-linked disorder that causes severe, progressive muscle loss and early death. In ~13% of patients, the disease is caused by a nonsense mutation (nm) in the gene for dystrophin. Ataluren is an orally delivered, investigational drug designed to promote ribosomal readthrough of premature stop codons in mRNA, leading to production of full-length, functional protein. A confirmatory Phase 3, multicenter, randomized, double-blind, placebo-controlled study has been designed to assess the efficacy and safety of ataluren 10, 10, 20 mg/kg tid in patients with nmDMD. The study design reflects lessons learned from prior studies and targets a study population to best demonstrate the treatment effect over 48 weeks.

Key study entry criteria require that patients are male with a nonsense mutation in the dystrophin gene, between the ages of 7 and 16 years, receiving a stable dose of corticosteroids, able to walk >150 m during the screening 6-min walk test (6MWT), and have a screening 6MWT below the protocol-specified threshold for %−predicted 6MWD. These criteria were selected based on the results of a retrospective subgroup analysis of patients in the Phase 2b trial of ataluren in nmDMD meeting these criteria, in which the difference between the 10, 10, 20 mg/kg dose of ataluren (n = 30) vs placebo (n = 31) in mean change in 6MWD over 48 weeks was ~50 m. In the planned study, 220 patients will be randomized in a 1:1 ratio to either placebo or ataluren. The primary outcome measure is the 6MWT. Secondary measures include: timed function tests, quality of life, North Star Ambulatory Assessment, patient/parent-reported activities of daily living, safety, compliance to study drug, and ataluren exposure of ataluren in blood.

This study will be the largest clinical trial of an investigational drug in DMD and is designed to confirm the treatment effect of ataluren seen in the Phase 2b ataluren trial.

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P.11.20

Results at 2 years of a phase IIb extension study of the exon-skipping drug eteplirsen in patients with DMD

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DMD is a rare, degenerative, genetic disease that results in progressive muscle loss and premature death. Affecting 1 in 5000 male births, DMD is caused by the inability to produce the dystrophin protein. There are no approved drugs available to treat DMD, although glucocorticoids show a modest effect with long-term efficacy limited by side effects. Eteplirsen is an investigational therapy designed to enable functional dystrophin production in boys who are amenable to exon 51-skipping therapy (~13%).

Twelve boys aged 7–13 years with eligible genotypes were randomized 1:1:1 to 30 mg/kg, 50 mg/kg, or placebo. Upon completion of a 24-week double-blind, placebo-controlled study phase, all subjects were enrolled in an open-label extension and the placebo-treated subjects initiated eteplirsen treatment. The critical clinical endpoint was the change in 6-min walk test (6MWT) distance from baseline compared to the placebo/delayed-treatment cohort.

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P.11.19

Phase 2b, dose-ranging study of ataluren (PTC124®) in nonsense mutation Duchenne muscular dystrophy – results of a post hoc analysis of change in %−predicted 6-min walk distance

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Duchenne muscular dystrophy (DMD) is a rare, X-linked disorder that causes severe, progressive muscle loss and early death. In ~13% of patients, the disease is caused by a nonsense mutation in the gene for dystrophin. Ataluren is an orally delivered, investigational drug designed to promote ribosomal readthrough of premature stop codons in mRNA, leading to production of full-length, functional protein. An international, multicenter, randomized, double-blind, placebo-controlled trial (Study 007) enrolled ambulatory males ≥5 years with nonsense mutation DMD. Patients received tid 20, 40 mg/kg ataluren; 10, 20, 40 mg/kg ataluren; or placebo orally for 48 weeks. The primary endpoint was absolute change in 6-min walk distance (6MWD) over 48 weeks. The study enrolled 174 subjects [median [range] age = 8 [5–20] years, median [range] height = 123 [99–173] cm] at 37 sites in 11 countries.

A post hoc analysis was performed to convert absolute 6MWD data to %−predicted 6MWD using a previously published age and height-based equation to adjust for maturational differences. Median [range] baseline %−predicted 6MWD = 63[12–96]%.

Mean decline in %−predicted 6MWD at Week 48 of 7.6% was observed for placebo, vs 2.7% for ataluren 10, 20, 40 mg/kg, resulting in a difference of 4.9% (nominal p−value = 0.0273). Mean decline for ataluren 20, 40 mg/kg was no different from placebo (7.7%), for a difference of 0.1% from placebo.

Conversion of absolute 6MWD data to %−predicted 6MWD assists in the interpretation of disease-related progressive loss of function against the background of normal growth and development. Analysis of Study 007 using %−predicted 6MWD data adjusts for maturational influences and supports the treatment difference between ataluren 10, 10, 20 mg/kg and placebo seen in the primary analysis of 6MWD in meters.

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