Viltolarsen (Viltepso; NS Pharma, Inc.)
FDA Approval Date: 8/12/2020

Safety and Dose Finding Study of NS-065/NCNO-01 in Boys with Duchenne Muscular Dystrophy (DMD). Clinicaltrials.gov
New Drug Review: Viltepso (viltolarsen) N. IPD Analytics. 2021

PIVOTAL TRIAL

Objectives	Evaluate the safety of a high (80 mg/kg) and low (40 mg/kg) dose of NS-065/NCNP-01 (Viltepso) delivered as an IV infusion in patients with Duchenne Muscular Dystrophy (DMD) amenable to exon 53 skipping. Other objectives include tolerability, muscle function and strength, pharmacokinetics and pharmacodynamics.
Methods	Phase II, multicenter, 2-period, randomized, placebo-controlled, dose finding study. Inclusion Criteria - 4 to 9 years, male, confirmed DMD mutation in dystrophin gene that is amenable to exon 53 skipping, able to walk independently without assistive devices, ability to complete time to stand, time to run/walk, and time to climb assessments, and stable dose of glucocorticoid for at least 3 months. Exclusion Criteria - acute illness within 4 weeks prior to first dose, evidence of symptomatic cardiomyopathy, severe allergy or hypersensitivity to medications, severe behavioral or cognitive problems that preclude participation in the study, previous or ongoing medical condition, medical history, physical findings or laboratory abnormalities that could affect safety, make it unlikely that treatment and follow-up be completed or impair assessment of study response, patients taking any other investigational drug within 3 months prior to start, patient has had surgery within 3 months prior to start, or patient has previously participated in this study or any other during Viltepso administration. Period 1 - double-blind, randomized ● Patients received weekly IV infusions of Viltepso 40 mg/kg or placebo for 4 weeks. Period 2 - open-label ● Patients received weekly IV infusion of Viltepso 40 mg/kg or 80 mg/kg for weeks 5-24 (20 weeks of active treatment).
Endpoints	Primary Endpoint - incidence of adverse events as assessed by CTCAE and dystrophin production by western blot. Secondary Endpoints - dystrophin production by RT-PCR for mRNA-percentage of exons skipped, dystrophin production by mass spectrometry, dystrophin production by immunofluorescence, muscle strength as measured by quantitative muscle testing (QMT), distance traveled in the 6-minute walk test (6MWT), time to climb 4 stairs, time to climb 4 stairs velocity, time to run/walk 10 meters, time to walk 10 meters velocity, time to stand, time to stand velocity, and North Star Ambulatory Assessment (NSAA) Score.
Results	Baseline Characteristics ● N = 16 ● 94% were white ● Median age ~ 7 years Efficacy ● Mean dystrophin levels increased from 0.6% (SD 0.8) of normal at baseline to 5.9% (SD 4.5) of normal by week 25, with a mean change in dystrophin of 5.3% (SD 4.5) of normal levels (p=0.01).

	● Median dystrophin level change from baseline - 3.8%. ● All patients demonstrated an increase in dystrophin levels over their baseline values. ● Improvement or stabilization of function over the 25-week period. ● Velocity in the time to run/walk 10M, the 6MWT, time to stand, time to climb 4 stairs, and the NSAA all significantly improved. Safety ● Most common adverse effects (≥ 15%) ○ Upper respiratory tract infection, injection site reaction, cough, and pyrexia ● No serious adverse events or discontinuation of therapy occurred.
Conclusion	Viltolarsen as an IV infusion in patients with DMD amenable to exon 53 skipping demonstrated de novo dystrophin production and clinical improvement in time function tests was observed.

Study to Assess the Efficacy and Safety of Viltolarsen in Ambulant Boys with DMD (RACER53). Clinicaltrials.gov
New Drug Review: Viltepso (viltolarsen) N. IPD Analytics. 2021
Clemens PR, Rao VK, Connolly AM, et al. Safety, Tolerability, and Efficacy of Viltolarsen in Boys with Duchenne Muscular Dystrophy Amenable to Exon 53 Skipping: A Phase 2 Randomized Clinical Trial. *JAMA Neurol.* 2020;77(8):982–991. doi:10.1001/jamaneurol.2020.1264

CONFIRMATORY TRIAL

Objectives	Evaluate the efficacy of viltolarsen compared to placebo in Duchenne Muscular Dystrophy (DMD) in patients amenable to exon 53 skipping.
Methods	Phase 3, double-blind, placebo-controlled, multicenter, randomized trial. Inclusion Criteria - 4 to 7 years, male, confirmed DMD mutation in the dystrophin gene that is amenable to exon 53 skipping, able to walk independently without assistive devices, TTSTAND <10 seconds, and stable dose of glucocorticoid for at least 3 months prior to study entry. Exclusion Criteria - current or history of chronic systemic fungal or viral infections, acute illness within 4 weeks prior to the first dose, evidence of symptomatic cardiomyopathy, allergy or hypersensitivity to study drug, severe behavioral or cognitive problems that preclude participation in the study, previous or ongoing medical condition, medical history, physical findings or laboratory abnormalities that could affect safety, make it unlikely that treatment and follow-up be completed or impair assessment of study response, surgery within the 3 months prior to first dose, positive test results for Hep B, Hep C, or HIV, currently taking any other investigational drug or within the previous 3 months, previously enrolled in a study with viltolarsen, currently taking any other exon skipping agent or within the previous 3 months, or having taken any gene therapy. Patients will be randomized to receive once weekly IV infusions of 80 mg/kg viltolarsen or placebo for up to 48 weeks.
Endpoints	Primary Endpoint - time to stand Secondary Endpoints - time to run/walk 10 meters, 6-minute walk test (6MWT), North Star Ambulatory Assessment (NSAA), time to climb 4 steps, and hand-held dynamometer
Results	Interim results have not been released yet.
Conclusion	Study is estimated to be completed in 2024.