News Release

Nightstar Therapeutics Announces Initiation of STAR Phase 3 Registrational Trial for NSR-REP1 in Choroideremia

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First-Ever Phase 3 Choroideremia Gene Therapy Trial

LEXINGTON, Mass. and LONDON, March 05, 2018 (GLOBE NEWSWIRE) -- Nightstar Therapeutics plc (NASDAQ:NITE), a clinical-stage gene therapy company developing treatments for rare inherited retinal diseases, today announced the initiation of the company's STAR Phase 3 registrational trial to study the safety and efficacy of NSR-REP1 in patients with choroideremia. In data from 32 patients treated with NSR-REP1 across four open-label Phase 1/2 clinical trials, over 90% of treated patients maintained or improved their visual acuity over a one-year follow-up period.

The STAR trial is expected to enroll approximately 140 patients across 18 clinical sites in the United States, Europe, Canada and South America, of which six sites will be surgical centers. Eligible patients will be randomized into one of three study arms: 56 patients receiving a high-dose of NSR-REP1 in one-eye (1.0 × 10^11 genome particles, or gp); 28 patients receiving a low-dose of NSR-REP1 in one-eye (1.0 × 10^10 gp); and 56 patients receiving no treatment (no-sham, parallel control arm). Patients in the STAR trial are expected to be recruited primarily from the existing Nightstar-sponsored natural history observational study (NIGHT study) in order to accelerate Phase 3 enrollment from this well-characterized patient population. The primary endpoint of the STAR trial is the proportion of patients with an improvement of at least 15 ETDRS letters from baseline in visual acuity at 12 months post-treatment. The primary endpoint will compare patients in the high-dose treatment arm with patients in the control arm.

"The initiation of this first-ever Phase 3 trial for the treatment of choroideremia is a major milestone for Nightstar and a tremendous step forward for patients otherwise at risk of blindness due to this devastating disease," said Dave Fellows, chief executive officer of Nightstar. "We are very encouraged by the responses we have seen to-date following treatment with NSR-REP1. This accomplishment demonstrates our team's ability to successfully advance important gene therapies. We are thankful to our academic and advocacy partners, as well as the many patients who have participated in our studies, all of whom have been instrumental in helping us to achieve this milestone."

"The Choroideremia Research Foundation is encouraged by the advancement of this gene therapy and congratulates the Nightstar team for their unrelenting commitment to serving patients," said Randy Wheelock, chief advisor for research and therapy development for the Choroideremia Research Foundation (CRF, **http://curechm.org/** (http://curechm.org/)).

Dr. Christopher Moen, president of the CRF commented, “Not only is this important for choroideremia patients and their families, but it is another important step toward developing therapies for the many people affected by blinding inherited retinal diseases, of which over 200 have been identified. The CRF is proud of its contributions in helping Nightstar achieve this milestone, including grants for initial research and preclinical studies. We look forward to realizing the full potential NSR-REP1 could have for patients with this challenging condition.”

About Choroideremia

Choroideremia, or CHM, is a rare, degenerative, X-linked genetic retinal disorder primarily affecting males, with no treatments currently available and represents a significant unmet medical need. CHM presents in childhood as night blindness, followed by progressive constriction of the visual fields, generally leading to vision loss in early adulthood and total blindness thereafter. Patients generally maintain good visual acuity until the degeneration encroaches onto the fovea, or the central part of the retina responsible for detailed vision. CHM is a degenerative disease that, starting at an early age, affects the retinal pigment epithelium, or RPE, which provides supportive biological functions for the photoreceptors and the underlying choroid, or outer retinal blood supply. Without a properly functioning RPE, the photoreceptors and the choroid slowly begin to atrophy, leading to vision loss. For CHM patients, it is often in middle age, when people typically are at or near their peak productive years, that visual impairment begins to limit independent activities of daily living and working productivity, generally leading to vision loss and total blindness thereafter. The prevalence of CHM is estimated to be one in 50,000 people, implying a total population of approximately 13,000 patients in the United States and the five major European markets.

CHM is caused by mutations in the CHM gene, which encodes REP1, a protein that plays a key role in intracellular protein trafficking and the elimination of waste products from retinal cells. Absence of functional REP1 leads to death of the RPE cells and degeneration of the overlying retina, which contains the retinal photoreceptors required to convert light into visual signals. Thus, the loss of REP1 function in retinal cells caused by CHM results in progressive vision loss and blindness.

About NSR-REP1 Gene Therapy

NSR-REP1 is comprised of an AAV2 vector containing recombinant human complementary DNA, or cDNA, that is designed to produce REP1 inside the eye. NSR-REP1 is administered surgically by injection into the sub-retinal space, which is between the outer layers of the retina. The introduction of a functional CHM gene into patients is intended to allow expression of REP1, thereby slowing or stopping the progression of CHM and the decline in vision. In addition, Nightstar believes that enhanced REP1 expression may also be able to slow or reverse the early stages of cell death in already damaged retinal cells, accounting for the substantial improvements in visual acuity that have been observed in some patients after treatment with NSR-REP1. Nightstar has received orphan drug designation for NSR-REP1 for the treatment of CHM from the U.S. Food and Drug Administration, or the FDA, in the United States and from the European Medicines Agency, or the EMA, in the European Union.

About Nightstar

Nightstar is a leading clinical-stage gene therapy company focused on developing and commercializing novel one-time treatments for patients suffering from rare inherited retinal diseases that would otherwise progress to blindness. Nightstar's lead product candidate, NSR-REP1, is currently in Phase 3 development for the treatment of patients with choroideremia, a rare, degenerative, genetic retinal disorder that has no current treatments and affects approximately one in every 50,000 people. Positive results from a Phase 1/2 trial of NSR-REP1 were published in **The Lancet** (https://www.globenewswire.com/Tracker?data=K07JMIxEg3s2L499sP7Bjy10MONZpty0UF4CLY_z3G62E5AO4oMx4j0TdR9RxdQ_lB-ned8ysGJYFdf1OD4IRjg7Bvm7IpW1SJ1QapRDkA2mvIFtKp-o6O725cPo5XSTjy7CsZejDaggPxvvCdIaWw==) in 2014 and in **The New England Journal of Medicine** (https://www.globenewswire.com/Tracker?data=ZAqI5e0Z6UadOlQwfgCyJvbkKKnfEwPGCbZWnvitinwbvP3T-GktiEfyuTwZSQQEom9bf6EvuRlqlqp6oD_z-fh-Gu96svi58tcv4ezCJq4uWvdYYOMBIO7romXh45JIrbOP4tSzpEDY0QW6udTwWQ==) in 2016. Nightstar's second product candidate, NSR-RPGR, is currently being evaluated in a Phase 1/2 clinical trial for the treatment of patients with X-linked retinitis pigmentosa, an inherited X-linked recessive retinal disease that affects approximately one in every 40,000 people.

For more information about Nightstar or its clinical trials, please visit **www.nightstartx.com** (https://www.globenewswire.com/Tracker?data=Rk1u5nLk2MpbsoGm4AKNiu0OsamauuBpXpAWI7aM_9zXbMUzagYtHdz7N-ol0p_7AF08opksiJXJsK7v1P6XvGZaLM9SvTK6Wjh4El8jf04=).

Forward-Looking Statements

This press release contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995, including, but not limited to: statements about our plans to develop and commercialize our product candidates, our STAR trial and other planned clinical trials, the clinical relevance and utility of the endpoints to be studied in the STAR trial, the prevalence of patient populations for our targeted indications, and the utility of prior preclinical and clinical data in determining future clinical results. These forward-looking statements are based on management's current expectations of future events and are subject to a number of involve substantial known and unknown risks, uncertainties and other factors that may cause our actual results, levels of activity, performance or achievements to be materially different from the information expressed or implied by these forward-looking statements, including the risks and uncertainties set forth in the "Risk Factors" section of our prospectus filed pursuant to Rule 424(b)(4) under the U.S. Securities Act of 1933, as amended, on September 28, 2017, and subsequent reports that we file with the U.S. Securities and Exchange Commission. We may not actually achieve the plans, intentions, estimates or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions, estimates and expectations disclosed in the forward-looking statements we make. The forward-looking statements in this press release represent our views as of the date hereof. We anticipate that subsequent events and developments will cause our views to change. However, while we may elect to update these forward-looking statements at some point in the future, we have no current intention

of doing so except to the extent required by applicable law. You should, therefore, not rely on these forward-looking statements as representing our views as of any date subsequent to the date of this press release.

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