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FORM 6-K

REPORT OF FOREIGN PRIVATE ISSUER
PURSUANT TO RULE 13a-16 OR 15d-16
UNDER THE SECURITIES EXCHANGE ACT OF 1934

For the Month of September 2018

Commission File Number: 001-38217

Nightstar Therapeutics plc
(Translation of registrant's name into English)

10 Midford Place, 2nd Floor
London W1T 5BJ United Kingdom
(Address of principal executive office)

Indicate by check mark whether the registrant files or will file annual reports under cover of Form 20-F or Form 40-F:

Form 20-F ☒ Form 40-F ☐

Indicate by check mark if the registrant is submitting the Form 6-K in paper as permitted by Regulation S-T Rule 101(b)(1): ☐

Indicate by check mark if the registrant is submitting the Form 6-K in paper as permitted by Regulation S-T Rule 101(b)(7): ☐

Preliminary Data from Dose Escalation Study in Phase 1/2 XIRIUS Trial of NSR-RPGR in X-linked Retinitis Pigmentosa

On September 22, 2018, Nightstar Therapeutics plc announced that positive preliminary safety and efficacy data of NSR-RPGR from the dose escalation study in the Phase 1/2 XIRIUS trial was presented at the EURETINA 2018 Congress.

A copy of the press release is attached as Exhibit 99.1 to this current report on Form 6-K and is incorporated by reference herein.

Exhibit	Description
99.1	Press Release dated September 22, 2018.

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

NIGHTSTAR THERAPEUTICS PLC

Date: September 24, 2018

By: /s/ Bryan Yoon
Name: Bryan Yoon
Title: General Counsel and Secretary

Exhibit 99.1

Nightstar Reports Positive Proof of Concept Data from Dose Escalation Study in XIRIUS Trial for NSR-RPGR in XLRP Patients

NSR-RPGR data presented at EURETINA 2018 Congress demonstrated proof of concept with durable dose-related improvements seen as early as month 1 across multiple microperimetry analyses

Preliminary efficacy signals observed in 3/3 patients in cohort 3 and 2/6 patients in cohorts 4 and 5, including durable improvements in overall macula sensitivity, central 16 macula sensitivity and number of improved macula loci

NSR-RPGR was well-tolerated with no dose limiting toxicities or serious treatment-related adverse events

XIRIUS expansion study planned to initiate in Q4 2018

Detailed results to be presented at R&D day on September 24, 2018

WALTHAM, Mass and LONDON, UK – September 22, 2018 (GLOBE NEWSWIRE) – Nightstar Therapeutics plc (NASDAQ:NITE), a clinical-stage gene therapy company developing treatments for rare inherited retinal diseases, today announced that positive preliminary safety and efficacy data of NSR-RPGR from the dose escalation study in the Phase 1/2 XIRIUS trial were presented today at the EURETINA 2018 Congress.

"We initiated this study last year, with the anticipation of demonstrating safety and stabilization of disease with NSR-RPGR, our codon-optimized gene therapy for XLRP," said Tuyen Ong, M.D., chief development officer of Nightstar. "Based on the preliminary findings of improved visual function as measured by microperimetry, we have established early proof of concept in XLRP, our second clinical program. As we move forward with the expansion study, we look forward to continuing to execute our clinical programs and sharing additional data on our XLRP program at future medical meetings."

XIRIUS is a Phase 1/2, open-label, dose-ranging, single-eye clinical trial consisting of a dose escalation study and an expansion study with sites in both the United States and the United Kingdom. The XIRIUS trial is intended to evaluate the safety, tolerability and efficacy of NSR-RPGR for the treatment of XLRP in patients with the RPGR mutation.

Enrollment of the dose escalation study in the XIRIUS trial was completed in August 2018, consisting of six cohorts of three patients each for a total of 18 adult patients. Each patient in the trial received a single sub-retinal injection of NSR-RPGR. Doses ranged from 5x10^9 genome particles (gp) in cohort 1 up to 5x10^11gp in cohort 6. One-year follow-up data on all 18 patients in the dose escalation study is expected to be available in the second half of 2019.

Preliminary NSR-RPGR Data from the Dose Escalation Study of XIRIUS Trial in XLRP

Safety and efficacy data were presented from the one-month follow-up for the first five cohorts. As of September 4, 2018, data through varying timepoints up to 12 months was available for the earlier cohorts. However, the one-month follow-up was the common timepoint for which the

complete set of safety and efficacy data was available for all patients in cohorts 1-5. One-month follow-up data were not yet available for cohort 6 as not all patients had completed their one-month visit. In addition to the one-month data for the first five cohorts, microperimetry data were presented for cohort 3 through the six-month follow-up visit.

Efficacy Summary: At the one-month follow-up after treatment with NSR-RPGR, all three patients in cohort 3 (5x10^10 gp), one of three patients in cohort 4 (1x10^11 gp) and one of three patients in cohort 5 (2.5x10^11 gp) experienced an improvement in microperimetry, as discussed further below. Among the patients in cohorts 4 and 5, improvements in microperimetry in the treated eyes were observed in those patients receiving a second course of steroids. The safety data and efficacy signals observed in the higher dose groups provided the basis for an early clinical proof of concept for the XIRIUS trial to progress to the expansion study.

All patients in cohort 3 (5x10^10 gp) showed an improvement in microperimetry endpoints at one, three and six months of follow-up after treatment with NSR-RPGR with general concordance across the various analyses described below. Efficacy signals were generally observed within one month and maintained through the six-month follow-up visit for patients in this cohort.

Microperimetry (MP): Microperimetry measures changes in visual function by gauging the ability to detect varying levels of light stimulus projected across the macula, the central part of the retina responsible for visual acuity. In the XIRIUS trial, microperimetry was measured on a grid of 68 points across the macula. Comparisons are made to baseline measurements in the treated eye as well as in comparison to the untreated eye.

- Overall Macula Sensitivity: Change in the average retinal sensitivity (in dB) of all 68 test loci. A responder analysis was also completed with a threshold of at least 2dB.
- Central 16 Sensitivity: Change in the average retinal sensitivity (in dB) from the 16 test loci closest to the center of the macula.
- Number of Improved Loci: The number of patients with at least a 5dB improvement in over 10% of loci (>= 7 loci).

The following table provides a summary of the microperimetry data observed in cohorts 1-5 at the one-month follow-up visit. Microperimetry data from the latest available timepoints for cohorts 1-5 (ranging from one month in cohort 5 through 12 months in cohort 1) were generally consistent with the one-month data presented below.

	Overall Macula Sensitivity *(Mean Change (dB) / # of Patients with ≥2dB Increase)*		***Central 16 Sensitivity*** *(Mean Change (dB))*		***Improved Loci*** *(# of Patients with ≥5dB Increase at ≥ 7 loci)*	
	Treated Eye	Untreated Eye	**Treated Eye**	Untreated Eye	**Treated Eye**	Untreated Eye
Cohort 1 (n=3)	+0.1 dB */0 pts*	+0.2 dB */0 pts*	+0.5 dB	+0.4 dB	0 pts	0 pts
Cohort 2* (n=2)	+0.2 dB */0 pts*	-0.8 dB */0 pts*	-0.1 dB	-0.8 dB	1 pts	0 pts
Cohort 3 (n=3)	+2.4 dB */3 pts*	-0.1 dB / *0 pts*	+6.1 dB	-1.0 dB	3 pts	0 pts
Cohort 4 (n=3)	+0.1 dB */1 pts*	-0.1 dB / *0 pts*	+1.2 dB	-0.2 dB	1 pts	0 pts
Cohort 5 (n=3)	+0.6 dB */1 pts*	+1.2 dB / *1 pts*	-0.6 dB	+1.4 dB	1 pts	1 pts

* One patient in cohort 2 was excluded from the analysis because triplicate testing was not performed at baseline.

The following table summarizes the changes in microperimetry observed from baseline through the six-month follow-up visit for cohort 3 using the three microperimetry analyses described above:

	Overall Macula Sensitivity *(Mean Change (dB) from Baseline)*		***Central 16 Sensitivity*** *(Mean Change (dB))*		***Improved Loci*** *(# of Patients with □5dB Increase at □ 7 loci)*	
	Treated Eye	Untreated Eye	**Treated Eye**	Untreated Eye	**Treated Eye**	Untreated Eye
Month 1	+2.4 dB	-0.1 dB	+6.1 dB	-1.0 dB	3 pts	0 pts
Month 3	+2.4 dB	-0.3 dB	+5.6 dB	-1.1 dB	3 pts	0 pts
Month 6	+2.3 dB	-0.5 dB	+5.1 dB	-1.2 dB	3 pts	0 pts

The efficacy data for cohort 3 was further analyzed using a histogram analysis, which revealed that the mean number of loci with retinal sensitivity improvements was consistently greater in the treated eyes as compared to the untreated eyes. Conversely, the mean number of loci with worsening retinal sensitivity was consistently greater in the untreated eyes as compared to the treated eyes for cohort 3.

Ellipsoid Zone (EZ): Ellipsoid zone measurements use optical coherence tomography to quantify the extent of undamaged photoreceptors remaining in the retina. No significant decreases in EZ from baseline were observed through the last follow-up visit for which data were available (ranging from one month in cohort 5 to 12 months in cohort 1). Due to the advanced stage of disease of patients enrolled in this dose escalation study, only two patients (one in cohort 2 and one in cohort 5) had a measurable baseline EZ that extended beyond the central 5 degrees of the macula. Prior natural history studies have shown that significant changes in EZ may require at least 1 year to 1.5 years to be detected, with follow-up visits on an annual basis being sufficient to detect progression. One-year follow-up data on all 18 patients in the dose escalation study is expected to be available in the second half of 2019. Nightstar plans to enroll patients into the expansion study with higher measurable baseline EZ to allow assessment and correlation of this anatomical endpoint with functional improvements in microperimetry.

Visual acuity (VA): Best corrected visual acuity was assessed using the clinically validated vision test chart developed for the Early Treatment of Diabetic Retinopathy Study (ETDRS). The mean baseline VA for treated eyes in patients in cohorts 1-5 ranged from 22 letters to 77 letters, while the mean baseline VA for untreated eyes ranged from 37 letters to 78 letters, respectively. At the latest follow-up timepoints for which data were available (ranging from three months in cohort 5 to 12 months in cohort 1), the visual acuity of 93% of patients in cohorts 1-5 was maintained within five ETDRS letters, or one line, of baseline in both the treated and untreated eyes.

Safety Summary: Available safety data (ranging from three months in cohort 5 to 12 months in cohort 1) from the 15 treated patients in cohorts 1-5 indicates that NSR-RPGR was well-tolerated. The safety profile in the dose escalation study is generally consistent with that of surgical vitrectomy procedures and what has been observed in clinical trials of other ocular

gene therapies. No serious adverse events related to treatment were reported and no early discontinuations or dose limiting toxicity were observed. Mild drug-related inflammation that potentially dampened efficacy was seen in the treated eyes of cohorts 4-5, with treatment efficacy observed to have been rescued in patients who received additional steroid treatment.

Adverse events of varying severity and duration related to the vitrectomy procedure or drug have been observed in the dose escalation study such as retinal changes, intraocular inflammation and visual disturbances.

The Data Monitoring Committee (DMC) reviewed preliminary safety data for cohorts 1-5 and recommended escalation to cohort 6. The DMC also has not restricted pediatric enrollment in either the dose escalation study or expansion study.

XIRIUS Expansion Study

Based on the totality of results to date, Nightstar expects to initiate enrollment of the expansion study in the XIRIUS trial in the fourth quarter of 2018. The expansion study is intended to enroll approximately 30 adult and pediatric patients at a therapeutic dose informed by the dose escalation study and a low-dose control group of approximately 15 patients. Preliminary efficacy data from the expansion study is expected to be available in mid-2019, with one-year follow-up data expected to be available in 2020.

R&D Webcast and Conference Call Information

Nightstar will host an R&D Day on Monday, September 24, with presentations beginning at 8:00 a.m., Eastern Time. The R&D Day will feature presentations on the preliminary NSR-RPGR data presented at EURETINA 2018 and Nightstar's other pipeline programs.

The R&D Day event will be webcast live under the investor relations section of Nightstar's website at ir.nightstartx.com. The dial-in details for the call are +1-877-491-5960 or +1-786 815-8441 (international), Conference ID: 1565326. To access the live webcast, please visit ir.nightstartx.com. A replay of the webcast will be available on the Nightstar website for two weeks following the conference.

About NSR-RPGR

NSR-RPGR is comprised of a standard AAV8 vector containing codon-optimized cDNA that is designed to produce human RPGR inside the eye. Nightstar has developed a codon-optimized gene that features RPGR protein expression levels up to four times higher than with a wild-type RPGR coding sequence. In addition, codon optimization provides greater sequence stability, which results in the consistent production of an identical protein product. NSR-RPGR is designed to produce RPGR-ORF15, the form of RPGR preferentially expressed in the retina.

About X-Linked Retinitis Pigmentosa (XLRP)

XLRP, a form of retinitis pigmentosa, is a rare inherited X-linked recessive genetic retinal disorder primarily affecting males. Approximately 70% of XLRP cases are due to variants in the genes responsible for the production of RPGR. RPGR is involved in the transport of proteins necessary for the maintenance of photoreceptor cells. Loss of RPGR function in the retinal cells causes the progressive loss of rod and cone photoreceptors, leading to the loss of vision experienced by patients. The estimated worldwide prevalence of XLRP due to RPGR variants is approximately one in 40,000 people, which translates to approximately 17,000 patients in the

United States and the five major European markets. There are no treatments currently available for XLRP. Nightstar is conducting a prospective, natural history observational study, referred to as the XOLARIS study, to better understand the progression of untreated XLRP in up to approximately 100 patients enrolled from approximately 23 centers in North America and Europe.

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 treatments currently available and affects approximately one in every 50,000 people. Positive results from a Phase 1/2 trials of NSR-REP1 were published in **The Lancet** in 2014 and in **The New England Journal of Medicine** in 2016.

For more information about Nightstar or its clinical trials, please visit **www.nightstartx.com**.

Cautionary Language Concerning Forward-Looking Statements

This press release contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. The words "believe," "anticipate," "could," "intend," "estimate," "will," "would," "may," "should," "project," "target," "track," "expect" or other similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. All statements contained in this press release other than statements of historical facts are forward-looking statements, including, without limitation: our planned and ongoing clinical trials for NSR-REP1 and NSR-RPGR, including our Phase 3 STAR trial in choroideremia and Phase 1/2 XIRIUS trial in X-linked retinitis pigmentosa; potential results and timelines relating to the dose escalation study in the XIRIUS trial and the planned expansion study in the XIRIUS trial; the potential utility of prior preclinical and clinical data and the data and endpoints presented herein in predicting future clinical results for our product candidates and any results of assessments to be conducted by regulatory agencies; the doses of NSR-RPGR to be used in the expansion study in the XIRIUS trial and future trials of NSR-RPGR; the continued clinical development of our pipeline; the timelines associated with our research and development programs including the timing of patient enrollment and the release of data from ongoing clinical trials and studies; the prevalence of patient populations for our targeted indications; and statements about our cash position and sufficiency of capital resources to fund our operating requirements, trends and other factors that may affect our financial results. These forward-looking statements are based on management's current expectations of future events as of the date of this release and are subject to a number of 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 those related to the timing and costs involved in commercializing any product candidate that receives regulatory approval; the initiation, timing and conduct of clinical trials; the availability of data from clinical trials and expectations for regulatory submissions and approvals; whether interim results of a clinical trial will be predictive of the final results of the trial; whether results of small or early stage clinical trials will be predictive of the results of later-stage trials; our scientific approach and general development progress; the availability or commercial potential of the our product candidates; the sufficiency of our cash resources; and other risks and uncertainties set forth in Item 3.D. "Risk Factors" section of our Annual Report on Form 20-F for the year ended

December 31, 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. We anticipate that subsequent events and developments will cause our views to change. We are under no duty to update any of these forward-looking statements after the date of this press release to conform these statements to actual results or revised expectations, except as required by 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. Any reference to our website address in this press release is intended to be an inactive textual reference only and not an active hyperlink.

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