FDA Approves Spark Therapeutics' LUXTURNA™ (voretigene neparvovec-rzyl), a One-time Gene Therapy for Patients with Confirmed Biallelic RPE65 Mutation-associated Retinal Dystrophy

LUXTURNA is first gene therapy for a genetic disease, first and only pharmacologic treatment for an inherited retinal disease (IRD) and first adeno-associated virus (AAV) vector gene therapy approved in U.S.

Children and adults living with IRD caused by biallelic RPE65 gene mutations nearly all progress to complete blindness

Spark Therapeutics to offer comprehensive patient support services for eligible patients in U.S.; will share details on access and price in early January

PHILADELPHIA, Dec. 19, 2017 (GLOBE NEWSWIRE) -- Spark Therapeutics (NASDAQ:ONCE), a fully integrated gene therapy company dedicated to challenging the inevitability of genetic disease, announced today that the U.S. Food and Drug Administration (FDA) has approved LUXTURNA™ (voretigene neparvovec-rzyl), a one-time gene therapy product indicated for the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy. LUXTURNA should only be administered to patients with mutations on both copies of the *RPE65* gene who have sufficient viable retinal cells as determined by their treating physicians.

LUXTURNA is the first FDA-approved gene therapy for a genetic disease, the first and only pharmacologic treatment for an inherited retinal disease (IRD) and the first adeno-associated virus (AAV) vector gene therapy approved in the U.S.

"Today's landmark approval of LUXTURNA is a moment decades in the making for the field of gene therapy, the inherited retinal disease (IRD) community, and most importantly, patients with biallelic *RPE65* mutation associated retinal dystrophy who now have the option to seek treatment," said Jeffrey D. Marrazzo, chief executive officer at Spark Therapeutics. "This one-time gene therapy for an inherited disease represents a first-of-its-kind breakthrough that may lay the groundwork for the development of gene therapies for other conditions that are not adequately addressed today. We offer our sincere gratitude to the patients and their families as well as the expert investigators who continue to participate in LUXTURNA's clinical development program."

"FDA approval of LUXTURNA represents a true paradigm shift for physicians caring for patients with hereditary retinal disease caused by biallelic *RPE65* mutations, who up until now have had no pharmacologic treatment options," said Alex V. Levin, M.D., MHSc, pediatric ophthalmologist and chief of the Wills Eye Pediatric Ophthalmology and Ocular Genetics Service in Philadelphia. "Now is the time for patients who have hereditary retinal disease, but lack a confirmed genetic diagnosis, to undergo genetic testing to determine, where appropriate, if mutations in the *RPE65* gene are responsible for their disease, and whether LUXTURNA may be an appropriate treatment option."

The U.S. Prescribing Information for LUXTURNA includes the following Warnings and Precautions: endophthalmitis; permanent decline in visual acuity; retinal abnormalities; increased intraocular pressure;

expansion of intraocular air bubbles; and cataract. LUXTURNA is not recommended for patients younger than 12 months of age because the retina is still growing, which may affect how LUXTURNA works. LUXTURNA is administered by subretinal injection to each eye on separate days within a close interval, but no fewer than 6 days apart. Please see the Indication and Important Safety Information section below for more information regarding risks associated with LUXTURNA.

LUXTURNA will be manufactured at Spark Therapeutics' manufacturing facility located in West Philadelphia, which is the first licensed manufacturing facility in the U.S. for a gene therapy treating an inherited disease. The gene therapy will be administered at selected treatment centers in the U.S. by leading retinal surgeons, who will receive surgical training provided by Spark Therapeutics on the administration procedure. LUXTURNA is expected to be available for administration in these treatment centers late in the first quarter of 2018. Spark Therapeutics is committed to ensuring eligible patients have access to LUXTURNA. More details on the company's patient support programs, its commitment to access, and the price of the product will be shared in early January.

"During the more than 12 years of innovative research with dedicated collaborators near and far, I've witnessed the dramatic improvement in vision in many patients who would have otherwise lost their sight," said Jean Bennett, the F.M. Kirby Professor of Ophthalmology in the Perelman School of Medicine at the University of Pennsylvania and Penn's Scheie Eye Institute. "I believe that the success of the LUXTURNA clinical development program will pave the way for the development of other gene therapies, that may help the millions of patients with genetic diseases who currently have limited or no treatment options."

"This approval is a watershed milestone," said Benjamin Yerxa, Ph.D., chief executive officer at the Foundation Fighting Blindness (FFB), a nonprofit organization focused on research for preventing and treating blindness caused by IRDs. "For people with an inherited retinal disease and for other patient communities, this decision may create important momentum for investigational gene therapies. The Foundation is very pleased that our early investments in research have helped lead to the approval of LUXTURNA. And we encourage patients to get genetic testing so they can help advance the research and possibly benefit from this treatment or other gene treatments as they emerge."

LUXTURNA was approved by FDA under Priority Review and previously received orphan drug and breakthrough therapy designations from FDA. With the approval of LUXTURNA, FDA will issue to Spark Therapeutics a Rare Pediatric Disease Priority Review Voucher for a Priority Review of a subsequent marketing application for a different product. Spark Therapeutics' Marketing Authorization Application (MAA) for LUXTURNA is currently under review with the European Medicines Agency (EMA). LUXTURNA also has received orphan product designations from EMA.

Genetic Testing and Obtaining a Genetic Diagnosis for Biallelic *RPE65* Mutation-associated Retinal Dystrophy

A genetic test is the only way to verify the gene mutation(s) that is the underlying cause of an inherited retinal disease (IRD), including those associated with biallelic *RPE65* mutations.

For people with IRDs, Spark Therapeutics will offer access to genetic testing designed to identify biallelic *RPE65* mutations. More information about the program and eligibility requirements will be available at www.luxturna.com.

Genetic testing is also available through a variety of other channels, including as a covered service through a patient's insurance, through non-profit organizations, as well as through various commercial labs.

Patient Support for Accessing LUXTURNA

Spark Therapeutics is committed to helping ensure that appropriate patients in the U.S. with a confirmed genetic diagnosis of biallelic *RPE65* mutation-associated retinal dystrophy have access to LUXTURNA. Spark has established Spark Therapeutics Generation Patient Services℠ to support appropriate patients, their families and providers in the U.S. through the LUXTURNA treatment experience. The team at Spark Therapeutics Generation Patient Services will assist eligible and enrolled patients navigate the insurance process and provide options to support travel and logistics to and from treatment centers.

For patients who are underinsured or are insured through government programs like Medicare and Medicaid, Spark plans to support independent Patient Assistance Programs that may help cover their drug and treatment costs.

More information will be available for patients and healthcare providers in the U.S. at www.mysparkgeneration.com or by calling 1-833-SPARK-PS (833-772-7577).

Indication and Important Safety Information

LUXTURNA (voretigene neparvovec-rzyl) is an adeno-associated virus vector-based gene therapy indicated for the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy.

Patients must have viable retinal cells as determined by the treating physicians.

Warnings and Precautions

Endophthalmitis may occur following any intraocular surgical procedure or injection. Use proper aseptic injection technique when administering LUXTURNA, and monitor for and advise patients to report any signs or symptoms of infection or inflammation to permit early treatment of any infection.

- **Permanent decline in visual acuity** may occur following subretinal injection of LUXTURNA. Monitor patients for visual disturbances.
- **Retinal abnormalities** may occur during or following the subretinal injection of LUXTURNA, including macular holes**,** foveal thinning, loss of foveal function, foveal dehiscence, and retinal hemorrhage. Monitor and manage these retinal abnormalities appropriately. Do not administer LUXTURNA in the immediate vicinity of the fovea. Retinal abnormalities may occur during or following vitrectomy, including retinal tears, epiretinal membrane, or retinal detachment. Monitor patients during and following the injection to permit early treatment of these retinal abnormalities. Advise patients to report any signs or symptoms of retinal tears and/or detachment without delay.
- **Increased intraocular pressure** may occur after subretinal injection of LUXTURNA. Monitor and manage intraocular pressure appropriately.
- **Expansion of intraocular air bubbles** Instruct patients to avoid air travel, travel to high elevations or scuba diving until the air bubble formed following administration of LUXTURNA has completely dissipated from the eye. It may take one week or more following injection for the air bubble to dissipate. A change in altitude while the air bubble is still present can result in irreversible vision loss. Verify the dissipation of the air bubble through ophthalmic examination.
- **Cataract** Subretinal injection of LUXTURNA, especially vitrectomy surgery, is associated with an increased incidence of cataract development and/or progression.

Adverse Reactions

- In clinical studies, ocular adverse reactions occurred in 66% of study participants (57% of injected eyes), and may have been related to LUXTURNA, the subretinal injection procedure, the concomitant use of corticosteroids, or a combination of these procedures and products.
- The most common adverse reactions (incidence ≥ 5% of study participants) were conjunctival hyperemia (22%), cataract (20%), increased intraocular pressure (15%), retinal tear (10%), dellen (thinning of the corneal stroma) (7%), macular hole (7%), subretinal deposits (7%), eye inflammation (5%), eye irritation (5%), eye pain (5%), and maculopathy (wrinkling on the surface of the macula) (5%).

Immunogenicity

Immune reactions and extra-ocular exposure to LUXTURNA in clinical studies were mild. No clinically significant cytotoxic T-cell response to either AAV2 or RPE65 has been observed. Study participants received systemic corticosteroids before and after subretinal injection of LUXTURNA to each eye, which may have decreased the potential immune reaction to either AAV2 or RPE65.

Pediatric Use

Treatment with LUXTURNA is not recommended for patients younger than 12 months of age, because the retinal cells are still undergoing cell proliferation, and LUXTURNA would potentially be diluted or lost during the cell proliferation. The safety and efficacy of LUXTURNA have been established in pediatric patients. There were no significant differences in safety between the different age subgroups.

Please see the full U.S. Prescribing Information for LUXTURNA here.

Clinical Trial Overview of LUXTURNA™ (voretigene neparvovec-rzyl)

The safety and efficacy of LUXTURNA were assessed in one open-label, dose-exploration Phase 1 safety study (n=12) and one open-label, randomized, controlled Phase 3 efficacy and safety study (n=31) in pediatric and adult participants (range 4 to 44 years) with biallelic *RPE65* mutation-associated retinal dystrophy and sufficient viable retinal cells.

Of the 31 participants enrolled in the Phase 3 study, 21 were randomized to receive subretinal injection of LUXTURNA and 10 were randomized to the control (non-intervention) group. One participant in the intervention group discontinued from the study prior to treatment and one participant in the control group withdrew consent and was discontinued from the study. All nine participants randomized to the control group elected to crossover and receive LUXTURNA after one year of observation. All participants in these studies continue to be followed for long-term safety and efficacy. LUXTURNA Phase 3 clinical trial data, including data from the intervention group of all randomized participants through the one-year time point has been previously reported in (*The Lancet*).

The efficacy of LUXTURNA in the Phase 3 study was established based on the multi-luminance mobility test (MLMT) score change from baseline to one year. MLMT was designed to measure changes in functional vision as assessed by the ability of a participant to navigate a course accurately and at a reasonable pace at seven different levels of illumination, ranging from 400 lux (corresponding to a brightly lit office) to one lux (corresponding to a moonless summer night). Each light level was assigned a score ranging from zero to six, with a higher score indicating that a participant could pass MLMT at a lower light level. A score of negative one was assigned to participants who could not pass MLMT at a light level of 400 lux. MLMT score change was defined as the difference between the score at baseline and the score at one year with a positive score change indicating that a participant was able to complete MLMT at a lower light level. Additional clinical outcomes included white light full-field light sensitivity threshold (FST) testing and visual acuity.

LUXTURNA Phase 3 clinical study results showed a statistically significant difference between the intervention group (n=21) and control participants (n=10) at one year in median bilateral MLMT score change (intervention minus control group difference of 2; *p*=0.001) and median first-treated eye MLMT score change (intervention minus control group difference of 2; *p*=0.003). After crossing over to receive LUXTURNA, participants in the control group showed a similar response to those in the intervention group. The median bilateral MLMT score change of two was observed for the intervention group at the 30-day timepoint. This change score has been sustained for at least three years for the original intervention group and at least two years in the crossover group in the Phase 3 clinical study. In addition, participants who received LUXTURNA showed a statistically significant improvement from baseline to one year in white light FST in the intervention group compared to the control group. The change in visual acuity from baseline to one year was not significantly different between the intervention and control participants.

The U.S. Prescribing Information for LUXTURNA includes the following Warnings and Precautions: endophthalmitis; permanent decline in visual acuity; retinal abnormalities; increased intraocular pressure; expansion of intraocular air bubbles; and cataract. The most common adverse reactions (incidence ≥ 5%) were conjunctival hyperemia, cataract, increased intraocular pressure, retinal tear, dellen (thinning of the corneal stroma), macular hole, subretinal deposits, eye inflammation, eye irritation, eye pain and maculopathy (wrinkling on the surface of the macula).

About *RPE65* Mutation-associated Inherited Retinal Disease (IRD)

Inherited retinal diseases (also known as inherited retinal dystrophies) are a group of rare blinding conditions caused by one of more than 220 different genes, often disproportionally affecting children and young adults. Based on Spark Therapeutics' assessment of available epidemiology data, the prevalent population in the U.S., Europe and select additional markets in the Americas and Asia/Pacific is up to approximately 6,000 individuals, in total, with biallelic *RPE65* mutations. It is estimated that between 1,000-2,000 people in the U.S. have vision loss due to these biallelic *RPE65* mutations. In addition, an expected 10-20 new patients a year are born with *RPE65* mutations in the U.S.

People living with IRD due to biallelic *RPE65* gene mutations nearly all progress to complete blindness. They often experience night blindness (nyctalopia) due to decreased light sensitivity in childhood or early adulthood and involuntary back-and-forth eye movements (nystagmus). As the disease progresses, individuals may experience loss in their peripheral vision, developing tunnel vision, and eventually, they may lose their central vision as well, resulting in total blindness. Independent navigation becomes severely limited, and vision-dependent activities of daily living are impaired. There are currently no approved pharmacologic treatment options for IRD due to biallelic *RPE65* gene mutations.

About Gene Therapy

Gene therapy is an approach to treat or prevent genetic disease by seeking to augment, replace or suppress one or more mutated genes with functional copies. It addresses the root cause of an inherited disease by enabling the body to produce a protein or proteins necessary to restore health or to stop making a harmful protein or proteins, with the potential of bringing back function in the diseased cells and/or slowing disease progression. To deliver the functional gene into the cell, a vector is used to transport the desired gene and is delivered either intravenously or injected into specific tissue. The goal is to enable, through the one-time administration of gene therapy, a lasting therapeutic effect.

About Spark Therapeutics

At Spark Therapeutics, a fully integrated company committed to discovering, developing and delivering gene therapies, we challenge the inevitability of genetic diseases, including blindness, hemophilia and neurodegenerative diseases. We have successfully applied our technology in the first FDA-approved gene therapy in the U.S. for a genetic disease, and currently have three programs in clinical trials, including product candidates that have shown promising early results in patients with hemophilia. At Spark, we see the path to a world where no life is limited by genetic disease. For more information, visit www.sparktx.com, and follow us on Twitter and LinkedIn.

Cautionary note on forward-looking statements

This release contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995, including statements regarding the company's product LUXTURNA™ (voretigene neparvovec-rzyl). The words "anticipate," "believe," "expect," "intend," "may," "plan," "predict," "will," "would," "could," "should," "continue" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Any forward-looking statements are based on management's current expectations of future events and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in, or implied by, such forward-looking statements. These risks and uncertainties include, but are not limited to, the risk that: (i) our MAA submitted for LUXTURNA may not be approved by EMA; (ii) the data from our Phase 3 clinical trial of LUXTURNA may not support EU labeling for all biallelic *RPE65* mutations other than Leber congenital amaurosis (LCA) or retinitis pigmentosa (RP); (iii) the improvements in functional vision demonstrated by LUXTURNA in our clinical trials may not be sustained over extended periods of time; and (iv) any one or more of our product candidates in preclinical or clinical development will not successfully be developed and commercialized. For a discussion of other risks and uncertainties, and other important factors, any of which could cause our actual results to differ from those contained in the forward-looking statements, see the "Risk Factors" section, as well as discussions of potential risks, uncertainties and other important factors, in our Annual Report on Form 10-K, our Quarterly Reports on Form 10-Q and other filings we make with the Securities and Exchange Commission. All information in this press release is as of the date of the release, and Spark undertakes no duty to update this information unless required by law.

Investor Relations Contact:

Ryan Asay
Ryan.asay@sparktx.com
(215) 239-6424

Media Contact:

Monique da Silva
communications@sparktx.com
(215) 282-7470

Photos accompanying this announcement are available at
http://www.globenewswire.com/NewsRoom/AttachmentNg/7f1ec1ed-0339-480c-b15a-c716748aecde
http://www.globenewswire.com/NewsRoom/AttachmentNg/9b4174fe-73d1-4e83-8430-c6b5840110fc

Videos accompanying this announcement are available at
http://www.globenewswire.com/NewsRoom/AttachmentNg/47574452-d56b-49d0-a460-e8e8e2f12c6e
http://www.globenewswire.com/NewsRoom/AttachmentNg/b92fa64f-83cf-4f1d-8e2e-2e42ead6be83

Source: Spark Therapeutics, Inc.