This guide is intended to provide basic information on different types of insurance plans. Spark® Therapeutics, Inc., makes no guarantees regarding coverage, assistance, or reimbursement of any product or service.

Always check your insurance policy for the most up-to-date information. Your policy may limit your participation in certain programs. You should not participate in any program if your policy prohibits it.
When you enroll in Spark Therapeutics Generation Patient Services℠, you are provided a dedicated team that provides personalized support. Your team includes a Patient Access Specialist (PAS) and a Patient Access Liaison (PAL), and each is committed to supporting you throughout your journey. Your PAS supports you over the phone or by email from the Patient Support Services Center. Your PAL is available over the phone, as well as to meet in person when needed.

Spark Therapeutics Generation Patient Services helps by:

- Providing a caring support team from confirmed diagnosis through postsurgery follow-up
- Helping you navigate insurance coverage and connecting you with financial assistance resources as needed
- Helping to coordinate your visits to the treatment center
- Answering any nonmedical questions you may have along the way

**Call toll-free:** 1-833-SPARK-PS (1-833-772-7577)

**Email:** MySparkGeneration@sparktx.com

**Web:** MySparkGeneration.com
WE ARE HERE TO SUPPORT YOU

The amount of information that you have to consider when pursuing treatment can be overwhelming. This is especially true when you are trying to understand insurance coverage and learning about financial assistance options. That’s where we come in. We are dedicated to helping you navigate the insurance process and connecting you to financial assistance resources for which you may be eligible.

This guide provides an overview of the different types of health insurance options that may be available to you. It also highlights the support and services you may be able to receive through Spark Therapeutics Generation Patient Services. The best sources of information about your insurance are your policy and insurance provider.
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INDICATION
LUXTURNAL (voretigene neparvovec-rzyl) is a prescription gene therapy product used for the treatment of patients with inherited retinal disease due to mutations in both copies of the RPE65 gene, which can only be confirmed through genetic testing. You must also have enough remaining cells in your retina (the thin layer of tissue in the back of your eyes) as determined by your healthcare professional.

IMPORTANT SAFETY INFORMATION
The following serious side effects may occur during or after the administration of LUXTURNA:

- Eye infections, including a serious infection inside of the eye called endophthalmitis, that may lead to blindness.
- Permanent decline in visual acuity, or the sharpness of central vision.

Please see additional Important Safety Information on pages 24-25 and accompanying US Full Prescribing Information for LUXTURNA.
UNDERSTANDING HEALTH INSURANCE OPTIONS

There is a variety of health insurance options that may cover some of the associated costs of treatment with LUXTURNA. This section provides details on health coverage options available in the United States.

COMMERCIAL (PRIVATE) HEALTH INSURANCE

Commercial health plans are also called private health plans. There are many different types of commercial health plans, each providing varying levels of coverage. You may get commercial health insurance from your employer or union, but you can also purchase it from a private insurance company or through the Affordable Care Act (ACA) health insurance exchange, sometimes called the marketplace.

Commercial health plans have different out-of-pocket costs, such as:

- Premiums
- Deductibles
- Co-pays
- Co-insurance

These plans may also have rules that set lower costs for services provided by in-network providers compared with out-of-network providers.

Call your health insurance provider to learn more about the services your plan covers. The number to call is generally on the back of your insurance card.
Marketplace plans help individuals, families, and small businesses shop for and enroll in appropriate health insurance plans. Each year, there is an open enrollment period when people can enroll in a plan.

- The open enrollment period typically runs from early November through mid-December
- Outside the open enrollment period, you can enroll during a special enrollment period if you qualify due to certain life events, such as divorce or legal separation, changes in residence, or:

Health insurance is available in every state, but the coverage and funding may vary, depending on the state. To get specific, up-to-date information on coverage and funding in your state and information on how to apply and enroll for health insurance, visit [www.healthcare.gov/marketplace-in-your-state](http://www.healthcare.gov/marketplace-in-your-state).
High-deductible health plan

This type of health plan has a higher deductible than a traditional insurance plan. The monthly premium is usually lower, but you pay more out of pocket up front before the insurance company pays its share. There are ways to help pay for the expenses in a high-deductible health plan. You may be eligible for a health reimbursement arrangement (HRA), in which your employer contributes a certain amount to each participating employee’s plan to be used toward medical expenses. Alternatively, health savings accounts (HSAs) allow you to deposit pretax money to pay for some medical expenses.

Tiered provider network

This type of plan categorizes doctors and hospitals based on the quality and cost of their patient care. For example, you may pay less if you are treated by a doctor who provides higher-quality healthcare for a lower cost.
**IMPORTANT TERMS TO KNOW**

**Balance billing:** The amount you may have to pay based on what your healthcare provider charges and what your insurance pays. Balance billing may be applicable if you use medical services outside your insurance network.

**Co-insurance:** The percentage of the cost you pay for healthcare services that are covered by your insurance.

**Co-pay:** The fixed amount you pay for healthcare services covered by your insurance.

**Commercial insurance:** This is a broad category of healthcare coverage. Benefits are privately purchased directly from a health plan or through an employer, a broker, or a health insurance exchange (also known as a health insurance marketplace). Individuals with private, commercial insurance may have a range of benefits.

**Deductible:** The specific amount of money that you must pay before your insurance company will pay for medical services if applicable.

**Health insurance exchange:** Also called a health insurance marketplace, this is a service available in every state that helps individuals, families, and small businesses obtain affordable health insurance.

**In-network provider:** Also known as a preferred provider, this is a provider who has contracted with your insurance company to accept negotiated rates. You may pay less for an in-network provider than an out-of-network provider.
Out-of-network provider: Also called a nonpreferred provider. This is any provider who is not in your healthcare plan’s network and may require you to pay higher out-of-pocket (OOP) costs if you use their services.

Out-of-pocket cost: This is the amount of money you may have to pay for the cost of covered healthcare services. OOP costs vary depending on the cost-sharing structure of the health plan.

Premium: The amount that must be paid every month by a family or individual to obtain coverage. If you have commercial insurance, your employer may pay all or a portion of your premium.

Self-insured plan: A type of insurance plan in which your employer collects premiums and takes on the responsibility of paying medical claims. Employers, usually larger companies, can contract for insurance services with a third-party administrator, or the plan can be self-administered.

Stop-loss: The dollar amount of claims for expenses at which point you’ve paid 100% of your OOP costs and your health insurance begins to pay 100%. Once you have paid the deductible and reached the OOP maximum, you have reached stop-loss.
### SEE HOW YOU’RE COVERED

<table>
<thead>
<tr>
<th>Has a network of providers?</th>
<th>Need a referral to see a specialist?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health Maintenance Organization (HMO)</td>
<td>YES ✓</td>
</tr>
<tr>
<td>Exclusive Provider Organization (EPO)</td>
<td>YES ✓</td>
</tr>
<tr>
<td>Preferred Provider Organization (PPO)</td>
<td>YES ✓</td>
</tr>
<tr>
<td>Point-of-Service (POS) Plan</td>
<td>YES ✓</td>
</tr>
</tbody>
</table>

The best source of information about your insurance is your policy and insurance company.
If out-of-network care is needed

<table>
<thead>
<tr>
<th>Health Maintenance Organization (HMO)</th>
<th>HMOs may cover out-of-network care if:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• None of the doctors in the HMO’s network has the experience to treat a certain health problem</td>
</tr>
<tr>
<td></td>
<td>• A network doctor refers you to an out-of-network doctor</td>
</tr>
<tr>
<td></td>
<td>• You have an emergency</td>
</tr>
</tbody>
</table>

| Exclusive Provider Organization (EPO) | There are no out-of-network benefits. EPOs may pay for out-of-network care if you have an emergency. |

| Preferred Provider Organization (PPO) | PPOs provide out-of-network care but may not pay for the full cost of treatment. If you choose to see an out-of-network doctor, you may have to pay for some of your treatment. |

| Point-of-Service (POS) Plan | POS plans provide out-of-network care, but your costs may be higher for out-of-network providers. |

This chart is meant to explain the structure of different plans and is not meant to guarantee coverage for particular situations.
GOVERNMENT-FUNDED HEALTH INSURANCE

Many people receive health insurance through a program that is funded by the state or federal government. Some of these programs include:

• Medicare
• Medicaid
• Children’s Health Insurance Program (CHIP)
• US Department of Defense (DoD)/TRICARE®

TRICARE is a registered trademark of the Department of Defense, Defense Health Agency. All rights reserved.
Medicare

Medicare is a health insurance program that covers people 65 years of age and older, as well as people younger than 65 who have certain disabilities. There are 4 parts to Medicare, each of which covers different healthcare services:

<table>
<thead>
<tr>
<th>Part A</th>
<th>Part B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital insurance that covers hospital stays, skilled nursing facilities, hospice care, and home healthcare.</td>
<td>People covered by Medicare who are receiving LUXTURNA would primarily benefit from Part B, which covers doctors’ services, diagnostic testing, outpatient and home healthcare, durable medical equipment, and preventive services.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Part C</th>
<th>Part D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Also called Medicare Advantage, Part C is offered by private companies approved by Medicare, and includes Parts A, B, and D as a bundle.</td>
<td>Prescription drug coverage for medications that are not typically administered in a doctor’s office or hospital.</td>
</tr>
</tbody>
</table>

IMPORTANT SAFETY INFORMATION (cont’d)

- Changes in the retina (the thin layer of tissue in the back of the eye) that can lead to vision loss including:
  - development of a hole, thinning, or loss of function of the retina, separation of the layers in the center of the retina, or bleeding in the retina.
  - breaks in or wrinkling on the surface of the retina or detachment of the retina.

Please see additional Important Safety Information on pages 24-25 and accompanying US Full Prescribing Information for LUXTURNA.
You may be eligible for Medicare if you have an inherited retinal disease (IRD) and a long enough work history but can no longer work because of your condition. To be enrolled in Medicare, you must first be approved for disability and then receive disability benefits from Social Security for more than 2 years.

Medicare does not cover all healthcare expenses. Additional insurance coverage, called a Medigap policy or Medicare Supplement Insurance, is available for additional cost. Medigap is private insurance that you can purchase to cover costs that Medicare does not cover and is available only if you have Medicare Parts A and B.

Please note, if you have Medicare Part C (Medicare Advantage), you are not eligible for a Medigap policy. By law, these 2 plans cannot be combined.

• The best time to buy a Medigap policy is during your 6-month open enrollment period after you enroll in Part B. If you do not purchase a Medigap policy during this time, it may not be available later or it may cost more
• Some states do not offer Medigap policies to Medicare recipients who are younger than 65
• If you have Medicare and would like to learn if your state offers a Medigap policy, contact Medicare directly or call your state’s insurance department
• To learn about disability benefits available through Social Security, call 1-800-772-1213 or visit ssa.gov

You may be eligible for Medicare if you have an inherited retinal disease (IRD) and a long enough work history but can no longer work because of your condition. To be enrolled in Medicare, you must first be approved for disability and then receive disability benefits from Social Security for more than 2 years.

To learn more about Medicare, contact 1-800-MEDICARE or visit Medicare.gov.
Medicaid

Medicaid provides low-cost or no-cost health coverage to millions of Americans, including:

- People with low income
- People with disabilities
- Pregnant women

If you qualify, Medicaid may be able to help you afford medical care for your IRD and other conditions by offering:

- Hospital visits
- Home healthcare
- Doctor and nurse visits
- Medical tests

Medicaid is administered by your state—meaning each state has different eligibility criteria for income, the number of people in your household, family status, and other factors. You can apply for Medicaid at any time of year.
Understanding commercial insurance and Medicaid together

Some people with an IRD who carry commercial insurance may also qualify for Medicaid. As a secondary policy, Medicaid may help offset the costs associated with a diagnosis like IRD.

If your commercial insurance plan does not cover certain medical costs or equipment, you may consider applying for Medicaid to help address those coverage limitations and exclusions. The first step in becoming eligible for Medicaid is obtaining an official verification of your disability from Social Security.

- In some states, if you are eligible for Supplemental Security Income (SSI) benefits because you have an IRD, you may be automatically enrolled in Medicaid
- If your state does not automatically enroll you in Medicaid, you may need to apply with another agency. Your Social Security office will direct you to the appropriate resources

Medicaid waiver programs

If you have an IRD, you may qualify for other Medicaid assistance not based solely on income. This can be done by obtaining a Medicaid waiver, which means the state Medicaid service waives the rules so that you can be eligible for Medicaid. A Medicaid waiver may help provide additional services and Medicaid coverage so that you can receive long-term care in your own community.

The federal government allows states to apply for waivers from the traditional Medicaid rules so they can offer additional assistance options. To learn more about waivers available in your state, visit Medicaid.gov/Medicaid, click on Section 1115 demonstrations, and select “State Waivers List.” Kidswaivers.org is another helpful resource to learn more about Medicaid waivers for children with disabilities.
How to apply for Medicaid

Contact your state Medicaid office to determine how to apply for Medicaid. You can find your state Medicaid office by visiting Medicaid.gov or by calling 1-877-267-2323 and following the prompts to get to the phone number for your state’s office.

Each state has different Medicaid application requirements, so you should check with your state office. Information you might be required to provide includes:

- Name and proof of age
- Information about current health insurance
- Documentation of disability
- Information about income from work and any other sources

To learn more about Medicaid, call 1-877-267-2323 or visit Medicaid.gov.
ADDITIONAL GOVERNMENT ASSISTANCE SERVICES

Supplemental Security Income

SSI is a federal income supplement program that helps adults with limited income and resources who are disabled, blind, or aged 65 or older, as well as blind or disabled children.

To qualify for SSI, you must have a condition with these characteristics:

- It causes serious functional limitations (child) or inability to earn more than a certain dollar amount per month (adult)
- It has lasted, or can be expected to last, for 12 months or more

An IRD is a condition that may fit some of the disability criteria for eligibility for SSI. You may be eligible for SSI if (not a complete list):

Your central visual acuity is

20/200 or less in your better eye when wearing corrective lenses

You have

Less than a 20 degree field of vision in your better eye

You have

20/200 in your better eye or less than or equal to 20 degrees in your better eye for at least 12 months when wearing corrective lenses

SSI is a federal income supplement program that helps adults with limited income and resources who are disabled, blind, or aged 65 or older, as well as blind or disabled children.

To qualify for SSI, you must have a condition with these characteristics:

- It causes serious functional limitations (child) or inability to earn more than a certain dollar amount per month (adult)
- It has lasted, or can be expected to last, for 12 months or more

An IRD is a condition that may fit some of the disability criteria for eligibility for SSI. You may be eligible for SSI if (not a complete list):
**Supplemental Security Income (cont’d)**

SSI also considers income and resources. If you are caring for a child under the age of 18 with an IRD, SSI will review your total household income to see if your child qualifies.

<table>
<thead>
<tr>
<th>What SSI assesses to see if you qualify</th>
<th>Description (not complete list)</th>
</tr>
</thead>
</table>
| **Income**                             | • Includes money you earn from work, Social Security benefits, pensions, and free food or shelter  
• Amount is set by each state |
| **Resources**                          | • Includes bank accounts, cash, investments such as stocks and bonds, and real estate  
• Does not include your current home and the land it is on, your primary vehicle, household goods, personal property (such as wedding rings), and any educational funds (such as grants or scholarships)  
• Limits for owned resources are $2,000 or less for an individual/child and $3,000 or less for a couple |
To apply for SSI benefits

For your child

If your child has an IRD, review the SSI Child Disability Starter Kit at ssa.gov/disability/disability_starter_kits_child_eng.htm. This kit provides answers to frequently asked questions about applying for SSI benefits for children with rare diseases and includes a worksheet that will help you gather the information you need.

To start the SSI application process, or to learn more about applying for SSI for your child, contact Social Security to determine if your income and resources are within the appropriate eligibility limits. You can call toll-free at 1-800-772-1213.
To apply for SSI benefits

For you

If you have an IRD and want to apply for Social Security disability insurance benefits, or learn more about the benefits, you can do so online at socialsecurity.gov or by calling 1-800-772-1213. If you call, a Social Security representative will make an appointment for you to apply during a separate telephone call or at a local Social Security office.

Once you are/your child is accepted for SSI, you may also be eligible for other government programs, such as Medicaid, food stamps, or more social services.

To learn more about SSI, visit socialsecurity.gov or call 1-800-772-1213.

Social Security Disability Insurance (SSDI)

SSDI is different from SSI. SSDI is funded through payroll taxes. You may be eligible for SSDI if you:

- Are considered disabled by the Social Security Administration (SSA)
- Are older than 18 years of age and younger than 65 years of age
- Have a history of paying social security payroll taxes and have earned enough “work credits”

Under SSDI, a disabled person’s spouse and children may be eligible to receive partial benefits.

To learn more about SSDI, visit ssa.gov/disabilityssi or call 1-800-772-1213.
**Children’s Health Insurance Program (CHIP)**

CHIP provides low-cost coverage for children if their families do not qualify for Medicaid and they cannot afford other health insurance. If your child has an IRD, he or she may be eligible for CHIP.

CHIP may help you afford medications and treatments for your child’s medical conditions by covering doctor visits, checkups, immunizations, prescriptions, dental and vision care, hospital visits, medical tests, X-rays, and emergency services.

Each state has its own CHIP program and its own rules about who qualifies. You can apply for CHIP any time of year. To find out if you qualify, call 1-800-318-2596 or fill out an application through your state’s health insurance exchange.

**TRICARE**

TRICARE is the health insurance program for uniformed service personnel and their families. National Guard/Reserve members, all active-duty members in the 7 uniformed services (Army, Navy, Air Force, Marines, Coast Guard, National Oceanic and Atmospheric Administration, and Public Health Service), retirees, family members and survivors of active-duty service members, and others who are registered in the Defense Enrollment Eligibility Reporting System (DEERS) are eligible for TRICARE.
INSURANCE AND FINANCIAL ASSISTANCE FOR LUXTURNA

If you have commercial insurance and are eligible
Spark® Therapeutics will help defray some out-of-pocket costs for LUXTURNA.

If you have government insurance
Spark can refer you to independent nonprofit organizations that may be able to help with your OOP costs. Referral does not guarantee a result; each foundation has its own rules for eligibility and assistance.

If you don’t have insurance
Your PAL will help explore available insurance options.

Give us a call at
1-833-SPARK-PS (1-833-772-7577)

IMPORTANT SAFETY INFORMATION (cont’d)
• Increased pressure inside of the eye. You should follow-up with your healthcare professional as instructed to detect and treat any increased pressure in the eye as this may cause blindness.
• Expansion of the air bubble formed in the eye after administration of LUXTURNA. You should avoid air travel, travel to high elevations, or scuba diving until your healthcare professional has told you that the air bubble formed in the eye following administration of LUXTURNA has disappeared. Engaging in these activities while the air bubble is present can cause permanent vision loss.

Please see additional Important Safety Information on pages 24-25 and accompanying US Full Prescribing Information for LUXTURNA.
INDICATION

LUXTURNA (voretigene neapavovec-rzyl) is a prescription gene therapy product used for the treatment of patients with inherited retinal disease due to mutations in both copies of the RPE65 gene, which can only be confirmed through genetic testing. You must also have enough remaining cells in your retina (the thin layer of tissue in the back of your eyes) as determined by your healthcare professional.

IMPORTANT SAFETY INFORMATION

The following serious side effects may occur during or after the administration of LUXTURNA:

• Eye infections, including a serious infection inside of the eye called endophthalmitis, that may lead to blindness.

• Permanent decline in visual acuity, or the sharpness of central vision.

• Changes in the retina (the thin layer of tissue in the back of the eye) that can lead to vision loss including:
  o development of a hole, thinning, or loss of function of the retina, separation of the layers in the center of the retina, or bleeding in the retina.
  o breaks in or wrinkling on the surface of the retina or detachment of the retina.

• Increased pressure inside of the eye. You should follow-up with your healthcare professional as instructed to detect and treat any increased pressure in the eye as this may cause blindness.

• Expansion of the air bubble formed in the eye after administration of LUXTURNA. You should avoid air travel, travel to high elevations, or scuba diving until your healthcare professional has told you that the air bubble formed in the eye following administration of LUXTURNA has disappeared. Engaging in these activities while the air bubble is present can cause permanent vision loss.

• Formation or worsening of cataract (clouding of the lens inside of the eye).

Please see accompanying US Full Prescribing Information for LUXTURNA.
IMPORTANT SAFETY INFORMATION (cont’d)

Tell your healthcare professional right away if you have any of the following symptoms of these serious side effects:

- Seeing floaters (specks that float about in your field of vision)
- Pain in the eye
- Any change in vision including decreased vision or blurred vision
- Seeing flashes of light

The following are the most common side effects that may occur with LUXTURNA:

- Redness of the eye
- Cataract (clouding of the lens inside of the eye)
- Increased pressure inside of the eye
- Breaks in the retina
- Dellen (thinning of the clear layer in the front of the eye)
- Development of a hole in the center of the retina
- Subretinal deposits (deposits under the retina)
- Eye swelling, irritation or pain
- Wrinkling on the surface of the center of the retina

Treatment with LUXTURNA is not recommended for patients younger than 12 months of age because the retina is still growing, which may affect how LUXTURNA works.

Because small quantities of LUXTURNA may be in your tears for a short period of time, for the first 7 days after administration of LUXTURNA, place any waste material from dressings, tears and nasal secretions in sealed bags prior to disposal.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088. You may also report side effects to Spark Therapeutics at 1-855-SPARKTX (1-855-772-7589).

This information does not take the place of talking to your healthcare professional about your medical condition or treatment. If you have questions about LUXTURNA after reading this information, ask your healthcare professional.

Please see accompanying US Full Prescribing Information for LUXTURNA.
HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LUXTURNA safely and effectively. See full prescribing information for LUXTURNA.

LUXTURNA (voretigene neparvovec-rzyl) intraocular suspension for subretinal injection
Initial U.S. Approval: 2017

-----------------------------INDICATIONS AND USAGE--------------------------
LUXTURNA is an adeno-associated virus vector-based gene therapy indicated for the treatment of patients with confirmed biallelic \textit{RPE65} mutation-associated retinal dystrophy. Patients must have viable retinal cells as determined by the treating physician(s). (1)

------------------------DOSAGE AND ADMINISTRATION----------------------
For subretinal injection only.

• The recommended dose of LUXTURNA for each eye is $1.5 \times 10^{11}$ vector genomes (vg), administered by subretinal injection in a total volume of 0.3 mL. (2.1)
• Perform subretinal administration of LUXTURNA to each eye on separate days within a close interval, but no fewer than 6 days apart. (2.1)
• Recommend systemic oral corticosteroids equivalent to prednisone at 1 mg/kg/day (maximum of 40 mg/day) for a total of 7 days (starting 3 days before administration of LUXTURNA to each eye), and followed by a tapering dose during the next 10 days. (2.1)

---------------------DOSAGE FORMS AND STRENGTHS----------------------
LUXTURNA is a suspension for subretinal injection, supplied in a 0.5 mL extractable volume in a single -dose 2 mL vial for a single administration in one eye. The supplied concentration (5x10^{12} vg/mL) requires a 1:10 dilution prior to administration. The Diluent is supplied in two single-use 2-mL vials. (3)

-------------------------------CONTRAINDICATIONS ------------------------------
None.

------------------------WARNINGS AND PRECAUTIONS-----------------------
• Endophthalmitis: Use proper aseptic injection technique and monitor for signs and symptoms of infection. (5.1)
• Permanent decline in visual acuity: Monitor for visual disturbances. (5.2)
• Retinal abnormalities: Monitor for macular abnormalities, retinal tears or breaks. Do not inject in the immediate vicinity of the fovea. (5.3)
• Increased intraocular pressure: Monitor and manage intraocular pressure elevations. (5.4)
• Expansion of intraocular air bubbles: Air travel and/or scuba diving is not recommended until any intraocular air bubbles have been absorbed. (5.5)
• Cataract: Subretinal injection of LUXTURNA may result in cataract formation or increase in the rate of cataract progression. (5.6)

-----------------ADVERSE REACTIONS ----------
The most common adverse reactions (incidence $\geq 5\%$) in the clinical trials 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). (6)

To report SUSPECTED ADVERSE REACTIONS, contact Spark Therapeutics, Inc. at 1-855-SPARKTX, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

--------------------------USE IN SPECIFIC POPULATIONS ---------------------
Pediatric use: Use in infants under 12 months of age is not recommended because of potential dilution or loss of LUXTURNA after administration due to the active retinal cells proliferation occurring in this age group. (8.4)

See 17 for PATIENT COUNSELING INFORMATION.
LUXTURNA (voretigene neparvovec-rzyl)

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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 physician(s).

2 DOSAGE AND ADMINISTRATION

For subretinal injection only.

2.1 Dose

- The recommended dose of LUXTURNA for each eye is 1.5 x 10^{11} vector genomes (vg), administered by subretinal injection in a total volume of 0.3 mL.
- Perform subretinal administration of LUXTURNA to each eye on separate days within a close interval, but no fewer than 6 days apart.
- Recommend systemic oral corticosteroids equivalent to prednisone at 1 mg/kg/day (maximum of 40 mg/day) for a total of 7 days (starting 3 days before administration of LUXTURNA to the first eye), and followed by tapering the dose during the following 10 days. The same corticosteroid dosing regimen applies for the administration of LUXTURNA to the second eye. If the corticosteroid taper following LUXTURNA administration to the first eye is not complete three days prior to the planned LUXTURNA administration to the second eye, then the corticosteroid regimen for the second eye replaces the taper for the first eye.

2.2 Preparation

Prepare LUXTURNA within 4 hours of administration using sterile technique under aseptic conditions in a Class II vertical laminar flow biological safety cabinet (BSC). Below is the list of items required for dilution and administration syringe preparation:

- One single-dose vial of Luxturna
- Two vials of Diluent
- One 3-mL sterile syringe
- One 20G 1-inch sterile needle
- Three 1-mL sterile syringes
- Three 27G ½-inch sterile needles
- Two sterile syringe caps
- One 10-mL sterile empty glass vial
- One sterile utility drape
- One sterile plastic bag
- Two sterile labels for administration syringes
- One sterile plain label
- One sterile skin marker

_Dilution of LUXTURNA_

1. Thaw one single-dose vial of LUXTURNA and two vials of Diluent at room temperature.
2. Mix the contents of the thawed Diluent vials by gently inverting them approximately 5 times.
3. Inspect the Diluent vials. If particulates, cloudiness, or discoloration are visible, do not use the vial(s); new vial(s) of Diluent should be used.

4. Obtain a 3-mL sterile syringe, a 20G 1-inch sterile needle, and a 10-mL sterile empty glass vial.

5. Using the 3-mL syringe with 20G 1-inch needle, transfer 2.7 mL of Diluent to the 10-mL glass vial. Dispose of the needle and syringe in an appropriate container.

6. Mix the contents of the thawed LUXTURNA single-dose vial by gently inverting approximately 5 times.

7. Inspect the LUXTURNA single-dose vial. If particulates, cloudiness, or discoloration are visible, do not use the vial; a new single-dose vial of LUXTURNA should be used.

8. Draw 0.3 mL of LUXTURNA into a 1-mL sterile syringe with a 27G ½-inch sterile needle. (Figure 1)

9. Transfer 0.3 mL of LUXTURNA to the glass vial containing 2.7 mL of Diluent from Step 5. Gently invert the 10-mL glass vial approximately 5 times to mix the contents.

10. Using the sterile plain label and sterile skin marker, label the 10-mL glass vial containing the diluted LUXTURNA as follows: ‘Diluted LUXTURNA’.

11. Remove all items from the BSC except the glass vial labeled ‘Diluted LUXTURNA’ and the sterile skin marker.

12. Re-sanitize the BSC prior to the next steps and place the glass vial and the sterile marker to the left side in the BSC.

**Preparation of LUXTURNA for Injection**

To keep the syringes sterile, two operators are required for transfer of the contents of the 10-mL glass vial labeled ‘Diluted LUXTURNA’ into each of two sterile 1-mL syringes.

13. Place a sterile utility drape, a sterile plastic bag, and two sterile labels into the BSC.

14. Place the sterile drape near the Primary Operator on the right side of the sanitized BSC surface, away from the diluted LUXTURNA.

15. The Secondary Operator unwraps two 1-mL syringes, two 27G ½-inch needles, and two syringe caps in the BSC, ensuring that the Primary Operator touches only sterile surfaces while transferring the items onto the sterile drape.

16. The Secondary Operator changes to a new pair of sterile gloves and stands or sits to the left of the Primary Operator. The Secondary Operator holds the 10-mL glass vial containing the diluted LUXTURNA (Figure 2a).
17. The Primary Operator withdraws 0.8 mL of the diluted LUXTURNA into a sterile 1-mL syringe using a 27G ½-inch sterile needle while the secondary operator holds the 10-mL glass vial. After the insertion of the needle, the Secondary Operator inverts the 10-mL glass vial enabling the Primary Operator to withdraw 0.8 mL without touching the 10-mL glass vial (Figure 2b).

18. The Primary Operator removes the needle and affixes a sterile cap to the sterile syringe, disposes of the needle in an appropriate container, and attaches a sterile label to the administration syringe.

19. The Primary Operator repeats Steps 17 and 18 to prepare a total of two administration syringes. Label the first syringe “Diluted LUXTURNA” and label the second syringe “Back-up Diluted LUXTURNA” using the sterile skin marker. The second syringe will serve as a backup for the surgeon performing the subretinal administration procedure. Discard the back-up syringe after surgery if not used.

20. Inspect both syringes. If particulates, cloudiness, or discoloration are visible, do not use the syringe.

21. Place the syringes into the sterile plastic bag after visual inspection and seal the bag.

22. Place the sterile plastic bag with syringes containing diluted LUXTURNA into an appropriate secondary container (e.g., hard plastic cooler) for delivery to the surgical suite at room temperature.
2.3 **Administration**

LUXTURNA should be administered in the surgical suite under controlled aseptic conditions by a surgeon experienced in performing intraocular surgery. In addition to the syringe containing the diluted LUXTURNA, the following items are required for administration:

- Subretinal injection cannula with a polyamid micro tip with an inner diameter of 41 gauge.
- Extension tube made of polyvinyl chloride no longer than 6” (15.2 cm) in length and with an inner diameter no greater than 1.4 mm.

![Figure 3. Injection Apparatus Assembly](image)

Follow the steps below for subretinal injection:

1. After confirming the availability of LUXTURNA, dilate the eye and give adequate anesthesia to the patient.
2. Administer a topical broad spectrum microbiocide to the conjunctiva, cornea and eyelids prior to surgery.
3. Inspect LUXTURNA prior to administration. If particulates, cloudiness, or discoloration are visible, do not use the product.
4. Connect the syringe containing the diluted LUXTURNA to the extension tube and subretinal injection cannula. To avoid excess priming volume, the extension tube should not exceed 15.2 cm in length and 1.4 mm in inner diameter. Inject the product slowly through the extension tube and the subretinal injection cannula to eliminate any air bubbles.
5. Confirm the volume of product available in the syringe for injection, by aligning the plunger tip with the line that marks 0.3 mL. (Figure 4)
6. After completing a vitrectomy, identify the intended site of administration. The subretinal injection cannula can be introduced via pars plana. (Figure 5a)

7. Under direct visualization, place the tip of the subretinal injection cannula in contact with the retinal surface. The recommended site of injection is located along the superior vascular arcade, at least 2 mm distal to the center of the fovea (Figure 5b), avoiding direct contact with the retinal vasculature or with areas of pathologic features, such as dense atrophy or intraretinal pigment migration. Inject a small amount of the product slowly until an initial subretinal bleb is observed. Then inject the remaining volume slowly until the total 0.3 mL is delivered.

8. After completing the injection, remove the subretinal injection cannula from the eye.

9. Following injection, discard all unused product. Dispose of the back-up syringe according to local biosafety guidelines applicable for handling and disposal of the product.

10. Perform a fluid-air exchange, carefully avoiding fluid drainage near the retinotomy created for the subretinal injection.

11. Initiate supine head positioning immediately in the post-operative period.

12. Upon discharge, advise patients to rest in a supine position as much as possible for 24 hours.
3 DOSAGE FORMS AND STRENGTHS

LUXTURNA is a suspension for subretinal injection, supplied in a 0.5-mL extractable volume in a 2-mL single-dose vial; the supplied concentration (5 x 10^{12} vg/mL) requires a 1:10 dilution prior to administration. The Diluent is supplied in two single-use 2 mL vials.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis

Endophthalmitis may occur following any intraocular surgical procedure or injection. Use proper aseptic injection technique when administering LUXTURNA. Following the injection, monitor patients to permit early treatment of any infection. Advise patients to report any signs or symptoms of infection or inflammation without delay.

5.2 Permanent decline in visual acuity

Permanent decline in visual acuity may occur following subretinal injection of LUXTURNA. Monitor patients for visual disturbances.

5.3 Retinal abnormalities

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. [see Dosage and Administration (2.3)]

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.

5.4 Increased intraocular pressure

Increased intraocular pressure may occur after subretinal injection of LUXTURNA. Monitor and manage intraocular pressure appropriately.

5.5 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.
5.6 Cataract

Subretinal injection of LUXTURNA, especially vitrectomy surgery, is associated with an increased incidence of cataract development and/or progression.

6 ADVERSE REACTIONS

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).

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of other products and may not reflect the rates observed in practice.

The safety data described in this section reflect exposure to LUXTURNA in two clinical trials consisting of 41 subjects (81 eyes) with confirmed biallelic RPE65 mutation-associated retinal dystrophy. Forty of the 41 subjects received sequential subretinal injections of LUXTURNA to each eye. One subject received LUXTURNA in only one eye. Seventy-two of the 81 eyes were exposed to the recommended dose of LUXTURNA at 1.5 x 10^{11} vg; 9 eyes were exposed to lower doses of LUXTURNA. Study 1 (n=12) was an open-label, dose-exploration safety study. Study 2 (n=29) was an open-label, randomized, controlled study for both efficacy and safety [(see Clinical Studies (14)]. The average age of the 41 subjects was 17 years ranging from 4 to 44 years. Of the 41 subjects, 25 (61%) were pediatric subjects under 18 years of age, and 23 (56%) were females.

Twenty-seven (27/41, 66%) subjects had ocular adverse reactions that involved 46 injected eyes (46/81, 57%). Adverse reactions among all subjects in Studies 1 and 2 are described in Table 1. Adverse reactions may have been related to voretigene neparvovec-rzyl, the subretinal injection procedure, the concomitant use of corticosteroids, or a combination of these procedures and products.
Table 1. Ocular Adverse Reactions Following Treatment with LUXTURNA (N=41)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Subjects n=41</th>
<th>Treated Eyes n=81</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any ocular adverse reaction</td>
<td>27 (66%)</td>
<td>46 (57%)</td>
</tr>
<tr>
<td>Conjunctival hyperemia</td>
<td>9 (22%)</td>
<td>9 (11%)</td>
</tr>
<tr>
<td>Cataract</td>
<td>8 (20%)</td>
<td>15 (19%)</td>
</tr>
<tr>
<td>Increased intraocular pressure</td>
<td>6 (15%)</td>
<td>8 (10%)</td>
</tr>
<tr>
<td>Retinal tear</td>
<td>4 (10%)</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>Dellen (thinning of the corneal stroma)</td>
<td>3 (7%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Macular hole</td>
<td>3 (7%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Subretinal deposits*</td>
<td>3 (7%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Eye inflammation</td>
<td>2 (5%)</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>Eye irritation</td>
<td>2 (5%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Eye pain</td>
<td>2 (5%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Maculopathy (wrinkling on the surface of the macula)</td>
<td>2 (5%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Foveal thinning and loss of foveal function</td>
<td>1 (2%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Endophthalmitis</td>
<td>1 (2%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Foveal dehiscence (separation of the retinal layers in the center of the macula)</td>
<td>1 (2%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Retinal hemorrhage</td>
<td>1 (2%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

*Transient appearance of asymptomatic subretinal precipitates inferior to the retinal injection site 1-6 days after injection

**Immunogenicity**

At all doses of LUXTURNA evaluated in Studies 1 and 2, immune reactions and extra-ocular exposure were mild. In Study 1 (n=12), the interval between the subretinal injections into the two eyes ranged from 1.7 to 4.6 years. In Study 2, the interval between the subretinal injections into the two eyes ranged from 7 to 14 days. No subject had a clinically significant cytotoxic T-cell response to either AAV2 or RPE65.

Subjects received systemic corticosteroids before and after subretinal injection of LUXTURNA to each eye. The corticosteroids may have decreased the potential immune reaction to either vector capsid (adeno-associated virus serotype 2 [AAV2] vector) or transgene product (retinal pigment epithelial 65 kDa protein [RPE65]).

**8 USE IN SPECIFIC POPULATIONS**

**8.1 Pregnancy**

**Risk Summary**

Adequate and well-controlled studies with LUXTURNA have not been conducted in pregnant women. Animal reproductive studies have not been conducted with LUXTURNA. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

**8.2 Lactation**

**Risk Summary**

There is no information regarding the presence of LUXTURNA in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be
considered along with the mother’s clinical need for LUXTURNA and any potential adverse effects on the breastfed infant from LUXTURNA.

8.3 Females and Males of Reproductive Potential

No nonclinical or clinical studies were performed to evaluate the effect of LUXTURNA on fertility.

8.4 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 cell proliferation.

The safety and efficacy of LUXTURNA have been established in pediatric patients. Use of LUXTURNA is supported by Study 1 and Study 2 [see Clinical Studies (14)] that included 25 pediatric patients with biallelic RPE65 mutation-associated retinal dystrophy in the following age groups: 21 children (age 4 years to less than 12 years) and 4 adolescents (age 12 years to less than 17 years). There were no significant differences in safety between the different age subgroups.

8.5 Geriatric Use

The safety and effectiveness of LUXTURNA have not been established in geriatric patients. Clinical studies of LUXTURNA for this indication did not include patients age 65 years and over.

11 DESCRIPTION

LUXTURNA (voretigene neparvovec-rzyl) is a suspension of an adeno-associated virus vector-based gene therapy for subretinal injection. LUXTURNA is a live, non-replicating adeno-associated virus serotype 2 which has been genetically modified to express the human RPE65 gene. LUXTURNA is derived from naturally occurring adeno-associated virus using recombinant DNA techniques.

Each single-dose vial of LUXTURNA contains 5 x 10^{12} vector genomes (vg) per mL, and the excipients 180 mM sodium chloride, 10 mM sodium phosphate, and 0.001% Poloxamer 188 (pH 7.3), in a 0.5-mL extractable volume. LUXTURNA requires a 1:10 dilution prior to administration. After dilution, each dose of LUXTURNA consists of 1.5 x 10^{11} vg in a deliverable volume of 0.3 mL.

The Diluent, supplied in 1.7 mL extractable volume per vial in two 2-mL vials, is composed of sterile water containing 180 mM sodium chloride, 10 mM sodium phosphate, and 0.001% Poloxamer 188 (pH 7.3). LUXTURNA may also contain residual components of HEK293 cells including DNA and protein and trace quantities of fetal bovine serum.

The product contains no preservative.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

LUXTURNA is designed to deliver a normal copy of the gene encoding the human retinal pigment epithelial 65 kDa protein (RPE65) to cells of the retina in persons with reduced or absent levels of biologically active RPE65. The RPE65 is produced in the retinal pigment epithelial (RPE) cells and converts all-trans-retinol to 11-cis-retinol, which subsequently forms the chomophore, 11-cis-retinal, during the visual (retinoid) cycle. The visual cycle is critical in phototransduction, which refers to the biological conversion of a photon of light into an electrical signal in the retina. Mutations in the RPE65 gene lead to reduced or absent levels of RPE65 isomerohydrolase activity, blocking the visual cycle and resulting in impairment of vision.
12.2 **Pharmacodynamics**

Injection of LUXTURNA into the subretinal space results in transduction of some retinal pigment epithelial cells with a cDNA encoding normal human RPE65 protein, thus providing the potential to restore the visual cycle.

12.3 **Pharmacokinetics**

**Biodistribution (within the body) and Vector Shedding (excretion/secration)**

LUXTURNA vector DNA levels in various tissues and secretions were determined using a quantitative polymerase chain reaction (qPCR) assay.

*Nonclinical data*

Biodistribution of LUXTURNA was evaluated at three months following subretinal administration in non-human primates. The highest levels of vector DNA sequences were detected in intraocular fluids (anterior chamber fluid and vitreous) of vector-injected eyes. Low levels of vector DNA sequences were detected in the optic nerve of the vector-injected eye, optic chiasm, spleen and liver, and sporadically in the lymph nodes. Vector DNA sequences were not detected in the gonads.

*Clinical data*

LUXTURNA vector shedding and biodistribution were investigated in a study measuring LUXTURNA DNA in tears from both eyes, and from serum, and whole blood of subjects in Study 2. In summary, LUXTURNA vector was shed transiently and at low levels in tears from the injected eye in 45% of the subjects in Study 2, and occasionally (7%) from the uninjected eye until Day 3 post-injection.

In 29 subjects who received bilateral administrations, LUXTURNA vector DNA was present in tear samples of 13 subjects (45%). Peak levels of vector DNA were detected in the tear samples on Day 1 post-injection, after which no vector DNA was detected in a majority of the subjects (8 of 13). Three subjects (10%) had vector DNA in tear samples until Day 3 post-injection, and two subjects (7%) had vector DNA in tear samples for around two weeks post-injection. In another two subjects (7%), vector DNA was detected in tear samples from the uninjected (or previously injected) eye until Day 3 post-injection. Vector DNA was detected in serum in 3/29 (10%) subjects, including two with vector DNA in tear samples up to Day 3 following each injection.

**Specific Populations**

No pharmacokinetic studies with LUXTURNA have been conducted.

**Drug Interaction Studies**

No interaction studies have been performed with LUXTURNA.

13 **NONCLINICAL TOXICOLOGY**

13.1 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

No animal studies have been conducted to evaluate the effects of LUXTURNA on carcinogenesis, mutagenesis, and impairment of fertility.

13.2 **Animal Toxicology and/or Pharmacology**

Bilateral, simultaneous subretinal administration of LUXTURNA was well tolerated at dose levels up to 8.25 x 10^{10} vg per eye in dogs with a naturally occurring RPE-65 mutation and 7.5 x 10^{11} vg (5 times higher than the recommended human dose level) per eye in non-human primates (NHPs) with normal-sighted eyes. In both animal models, bilateral, sequential subretinal administrations, where the contralateral eye was injected
following the first eye, were well tolerated at the recommended human dose level of $1.5 \times 10^{11}$ vg per eye. In addition, dogs with the RPE-65 mutation displayed improved visual behavior and pupillary responses. Ocular histopathology showed only mild changes, which were mostly related to healing from the surgical administration procedure. Other findings observed following subretinal injection of LUXTURNA in dogs and NHPs included occasional and isolated inflammatory cells in the retina, with no apparent retinal degeneration. Dogs not previously exposed to AAV2 vectors developed antibodies to the AAV2 capsid following a single administration of LUXTURNA, whereas NHPs did not.

14 CLINICAL STUDIES

The efficacy of LUXTURNA in pediatric and adult patients with biallelic RPE65 mutation-associated retinal dystrophy was evaluated in an open-label, two-center, randomized trial (Study 2). Of the 31 enrolled subjects, 21 subjects were randomized to receive subretinal injection of LUXTURNA. One subject discontinued from the study prior to treatment. Ten subjects were randomized to the control (non-intervention) group. One subject in the control group withdrew consent and was discontinued from the study. The nine subjects who were randomized to the control group were crossed over to receive subretinal injection of LUXTURNA after one year of observation. The average age of the 31 randomized subjects was 15 years (range 4 to 44 years), including 64% pediatric subjects (n=20, age from 4 to 17 years) and 36% adults (n=11). The 31 randomized subjects included 13 males and 18 females. Sixty-eight percent (68%) of the subjects were White, 16% were Asian, 10% were American Indian or Alaska Native, and 6% were Black or African-American. Bilateral subretinal injections of LUXTURNA were administered sequentially in two separate surgical procedures with an interval of 6 to 18 days.

The efficacy of LUXTURNA was established on the basis of multi-luminance mobility testing (MLMT) score change from Baseline to Year 1. The MLMT was designed to measure changes in functional vision, as assessed by the ability of a subject to navigate a course accurately and at a reasonable pace at different levels of environmental illumination. The MLMT was assessed using both eyes and each eye separately at one or more of seven levels of illumination, ranging from 400 lux (corresponding to a brightly lit office) to 1 lux (corresponding to a moonless summer night). Each light level was assigned a score code ranging from 0 to 6. A higher score indicated that a subject was able to pass the MLMT at a lower light level. A score of 1 was assigned to subjects who could not pass MLMT at a light level of 400 lux. The MLMT of each subject was videotaped and assessed by independent graders. The MLMT score was determined by the lowest light level at which the subject was able to pass the MLMT. The MLMT score change was defined as the difference between the score at Baseline and the score at Year 1. A positive MLMT score change from Baseline to Year 1 visit indicated that the subject was able to complete the MLMT at a lower light level.

Additional clinical outcomes were also evaluated, including full-field light sensitivity threshold (FST) testing, visual acuity, and visual fields.

Table 2 summarizes the median MLMT score change from Baseline to Year 1 in the LUXTURNA treatment group as compared to the control group. A median MLMT score of 2 or greater was observed in the LUXTURNA treatment group, while a median MLMT score change of 0 was observed in the control group, when using both eyes or the first-treated eye. An MLMT score change of two or greater is considered a clinically meaningful benefit in functional vision.
Table 2. Efficacy Results of Study 2 at Year 1, Compared to Baseline

<table>
<thead>
<tr>
<th>Efficacy Outcomes</th>
<th>LUXTURNA n=21</th>
<th>Control n=10</th>
<th>Difference (LUXTURNA minus Control)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLMT score change for bilateral eyes, median (min, max)</td>
<td>2 (0, 4)</td>
<td>0 (-1, 2)</td>
<td>2</td>
<td>0.001</td>
</tr>
<tr>
<td>MLMT score change for first-treated eye, median (min, max)</td>
<td>2 (0, 4)</td>
<td>0 (-1, 1)</td>
<td>2</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Table 3 shows the number and percentage of subjects with different magnitudes of MLMT score change using both eyes at Year 1. Eleven of the 21 (52%) subjects in the LUXTURNA treatment group had an MLMT score change of two or greater, while one of the ten (10%) subjects in the control group had an MLMT score change of two.

Table 3. Magnitude of MLMT Score Change Using Both Eyes at Year 1 (Study 2)

<table>
<thead>
<tr>
<th>Score Change</th>
<th>LUXTURNA n=21</th>
<th>Control n=10</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1</td>
<td>0</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>0</td>
<td>2 (10%)</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>1</td>
<td>8 (38%)</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>2</td>
<td>5 (24%)</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>3</td>
<td>5 (24%)</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>1 (4%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Figure 6 shows MLMT performance of individual subjects using both eyes at Baseline and at Year 1.
Figure 6. MLMT Score Using Both Eyes at Baseline and One Year for Individual Subjects

Note for Figure 6: *subjects who were withdrawn or discontinued. The open circles are the baseline scores. The closed circles are the Year 1 scores. The numbers next to the solid circle represent score change at Year 1. The horizontal lines with arrows represent the magnitude of the score change and its direction. Arrows pointing towards the right represent improvement. The top section shows the results of the 21 subjects in the treatment group. The bottom section shows the results of the 10 subjects in the control group. Subjects in each group are chronologically organized by age, with the youngest subject at the top and the oldest subject at the bottom.

Analysis of white light FST testing showed statistically significant improvement from Baseline to Year 1 in the LUXTURNA treatment group compared to the control group. The change in visual acuity from Baseline to Year 1 was not significantly different between the LUXTURNA and control groups.

Figure 7 shows the effect of LUXTURNA over the two-year period in the LUXTURNA treatment group, as well as the effect in the control group after crossing over to receive subretinal injection of LUXTURNA. A median MLMT score change of two was observed for the LUXTURNA treatment group at Day 30, and this effect was sustained over the remaining follow-up visits throughout the two-year period. For the control group, a median MLMT score change of 0 was observed at all four follow-up visits during the first year. However, after crossing-over to receive subretinal injection of LUXTURNA, the subjects in the control group showed a similar response to LUXTURNA as compared to the subjects in the LUXTURNA treatment group.
Note for Figure 7: Each box represents the middle 50% of distribution of MLMT score change. Vertical dotted lines represent additional 25% above and below the box. The horizontal bar within each box represents the median. The dot within each box represents the mean. The solid line connects the mean MLMT score changes over visits for the treatment group, including five visits during the first year and one visit at Year 2 (marked as x365). The dotted line connects the mean MLMT score change over visits for the control group, including five visits during the first year without receiving LUXTURNA, and four visits within the second year (marked as x30, x90, x180, and x365) after cross-over at Year 1 to receive LUXTURNA.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each carton of LUXTURNA (NDC 71394 – 415-01) contains one single-dose vial of the LUXTURNA (NDC 71394 – 065-01, 0.5 mL extractable volume) and two vials of Diluent (NDC 71394 – 716-01, 1.7 mL extractable volume in each vial). LUXTURNA contains 5 x 10^{12} vector genomes (vg) per mL, requires a 1:10 dilution prior to administration.

Store LUXTURNA and Diluent frozen at ≤ -65 °C.

Following thaw of the vials, store at room temperature. Store diluted LUXTURNA at room temperature [See Dosage and Administration 2.2].

LUXTURNA is an adeno-associated virus vector-based gene therapy. Follow universal biohazard precautions for handling.

17 PATIENT COUNSELING INFORMATION

Advise patients and/or their caregivers of the following risks.

• Endophthalmitis and other eye infections
  Serious infection can occur inside of the eye and may lead to blindness. In such cases, there is an urgent need for management without delay. Advise patients to call their healthcare provider if they experience new floaters, eye pain, or any change in vision.

• Permanent decline in visual acuity
  Permanent decline in visual acuity may occur following subretinal injection of LUXTURNA. Advise patients to contact their healthcare provider if they experience any change in vision.

• Retinal abnormalities
Treatment with LUXTURNA may cause some defects in the retina such as a small tear or a hole in the area or vicinity of the injection. Treatment may cause thinning of the central retina or bleeding in the retina. Advise patients to follow up with their healthcare provider on a regular basis and report any symptoms such as decreased vision, blurred vision, flashes of light, or floaters in their vision without delay.

- **Increased intraocular pressure**
  Treatment with LUXTURNA may cause transient or persistent increase in intraocular pressure. If untreated, such increases in intraocular pressure may cause blindness. Advise patients to follow-up with their healthcare provider to detect and treat any increase in intraocular pressure.

- **Expansion of intraocular air bubbles**
  Advise 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. A change in altitude while the air bubble is still present may cause irreversible damage.

- **Cataract**
  Advise patients that following treatment with LUXTURNA, they may develop a new cataract, or any existing cataract may get worse.

- **Shedding of LUXTURNA**
  Transient and low level shedding of LUXTURNA may occur in patient tears. Advise patients and/or their caregivers on proper handling of waste material generated from dressing, tears and nasal secretion, which may include storage of waste material in sealed bags prior to disposal. These handling precautions should be followed for up to 7 days following LUXTURNA administration.

Manufactured by:
Spark Therapeutics, Inc.
3737 Market Street
Philadelphia, PA 19104

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