Product: LUXTURNA

Proper Name: Voretigene neparvovec-rzyl

Indication: It 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).

Description: LUXTURNA (voretigene neparvovec-rzyl) is a recombinant adeno-associated virus serotype 2 (AAV2) vector with a cytomegalovirus (CMV) enhancer and chicken beta actin (CβA) promoter driving expression of the gene for human retinal pigment epithelium 65 kDa protein (hRPE65), which is an isomerohydrolase converting all-trans-retinyl ester to 11-cis-retinol in the retinoid visual cycle.

BLA: STN 125610

Regulatory Milestone:

Date	Milestones
IND	
9/20/2005	Pre-IND meeting
6/14/2007	IND 13408 submission by sponsor of Children's Hospital of Philadelphia
6/24/2008	Orphan drug designation of AAV2-hRPR65v2 for treatment of Leber congenital amaurosis due to RPE65 mutation (LCA2) (#08-2593)
12/18/2008	End of Phase 1 type B meeting to discuss a Phase 3 design
1/13/2010	Special Protocol assessment (SPA) Request; sponsor later withdrew request
9/8/2010	Type C meeting to discuss mobility test as primary efficacy endpoint
5/10/2011 & 10/2/2014	Type C meeting to discuss CMC issues in support of Phase 3 trial
6/29/2011	FDA Cellular, Tissue, and Gene Therapies Advisory Committee meeting: Cellular and Gene Therapies for Retinal Disorders (general discussion, not on specific products)
4/24/2012	Clinical hold due to SAE of endophthalmitis

1/13/2014	Transfer of IND 13408 from the Center for Cellular and Molecular Therapeutics, Children's Hospital of Philadelphia (CHOP) to Spark Therapeutics
9/24/2014	Sponsor received Breakthrough Therapy Designation for treatment of nyctalopia (night blindness) in patients with Leber congenital amaurosis due to RPE65 mutation
Pre-BLA	
1/15/2015	Type C meeting to discuss the adequacy of nonclinical data in support of a BLA submission
6/16/2015	Type C meeting to discuss the indication, diagnosis, primary endpoint analysis, and clinical data submission in preparation for a BLA submission
7/21/2015	Advice on Statistical Analysis Plan of Phase 3 protocol
3/18/2015	Orphan Drug designation granted for treatment of retinitis pigmentosa due to autosomal recessive RPE65 gene mutations
3/25/2016	Pre-BLA meeting to discuss a rolling BLA submission and priority review status
11/29/2016	Orphan-Drug designation granted for the use of "adeno-associated viral vector type 2 expressing human recombinant retinal pigment epithelial 65KDa protein gene for the treatment of inherited retinal dystrophy due to biallelic RPE65 mutations."
BLA Submission	
4/26/2016	BLA rolling submission part 1: Nonclinical information
2/21/2017	BLA rolling submission part 2: Clinical information
5/16/2017	BLA rolling submission part 3: CMC information
7/14/2017	Accepted for filing; Priority review; Pediatric Rare Disease Designation
10/12/2017	Advisory Committee Meeting to discuss safety and efficacy of BLA 125610
1/12/2018	PDUFA Goal Date

FDA Approval: December 19, 2017

EMA approval: September 22, 2018

Health Canada approval: October 15, 2020

Australian Therapeutics Goods Administration (TGA) approval: August 4, 2020

Package Insert: LUXTURNA

Summary Basis for Regulatory Approval: December 18, 2017 Summary Basis for Regulatory Action - LUXTURNA

European Public Assessment Report: September 20, 2018 Assessment Report - LUXTURNA

Manufacturing Platform:

PARAMETER	DATA	REFERENCE
Manufacturer	Spark Therapeutics, Inc.	
Transgene	Retinal pigment epithelial 65 kDa protein [RPE65]	1
Indication	It 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).	3
Virus and Serotype	Adeno-associated virus serotype 2 (AAV2)	2
Cell Substrate	Mammalian cell-substrate	3
Manufacturing platform	Transient transfection	3
Dose in vial/final container	5×10^{12} vector genomes (vg) per mL (0.05 mg vector/ml)	1
Dose / patient	1.5×10^{11} vector genomes (vg), administered by subretinal injection in a total volume of 0.3 mL for each eye.	1

1. Package insert: Package Insert - LUXTURNA
2. EPAR full: Luxturna : EPAR - Public assessment report
3. EPAR quality: Luxturna : EPAR - Public assessment report (page 11)
4. FDA SBAR – quality: Summary Basis for Regulatory Action - LUXTURNA

Advisory Committee:

A meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) was held on October 12, 2017 to provide feedback to FDA regarding clinical efficacy and safety, and an overall benefit-risk assessment of LUXTURNA.

Summary of discussion:

- A 2-light level improvement in MLMT (i.e., an MLMT score change of 2) is clinically meaningful.
- The potential risks associated with subretinal injection of LUXTURNA and concomitant corticosteroid use are acceptable for the pediatric population, even in the very young population.
- The retinal cellular proliferation is not complete until 8 to 12 months of age, and LUXTURNA may be diluted or lost during the cellular proliferation process.
- Further study may be needed to support repeat administration of previously treated eyes if the efficacy of LUXTURNA declines over time.
- The Committee voted 16 (Yes) to 0 (No) to the question, "Considering the efficacy and safety information provided in the briefing document, as well as the presentations and discussions during the AC meeting, does voretigene neparvovec-rzyl have an overall favorable benefit-risk profile for the treatment of patients with vision loss due to confirmed biallelic RPE65 mutation-associated retinal dystrophy?"

Safety:

The pharmacovigilance and clinical review team recommended that the applicant revise the voluntary registry study to include ophthalmological examinations to collect more data on

safety. Based on review of available data, and input from FDA's Center for Drugs Evaluation and Research (CDER) and the Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) meeting, the pharmacovigilance and clinical review team concludes that the safety concerns from the Phase 1 and Phase 3 studies can be mitigated through routine medical practice, adequate Prescribing Information as well as the voluntary post-marketing plans proposed by the applicant. The reviewed safety data do not substantiate a need for a Risk Evaluation and Mitigation Strategies (REMS), a safety post-marketing requirement (PMR) study, or a safety post-marketing commitment (PMC) study.

Clinical Trials:

NCT	TRIAL PHASE	SUBJECTS ENROLLED	STUDY TITLE	COUNTRIES
NCT00516477	1	12	Safety Study in Subjects with Leber Congenital Amaurosis	United States
NCT01208389	1, 2	12	Phase 1 Follow-on Study of AAV2-hRPE65v2 Vector in Subjects with Leber Congenital Amaurosis (LCA) 2	United States
NCT00999609	3	31	Safety and Efficacy Study in Subjects with Leber Congenital Amaurosis	United States

EudraCT Number: Not available

Publications:

- Rodrigues, G. A., Shalaev, E., Karami, T. K., Cunningham, J., Slater, N., & Rivers, H. M. (2018). Pharmaceutical Development of AAV-**Based Gene Therapy Products for the Eye.** Pharmaceutical research, 36(2), 29. https://doi.org/10.1007/s11095-018-2554-7
- Nidetz, N. F., McGee, M. C., Tse, L. V., Li, C., Cong, L., Li, Y., & Huang, W. (2020). **Adeno-associated viral vector-mediated immune responses: Understanding barriers to**

gene delivery. Pharmacology & therapeutics, 207, 107453. https://doi.org/10.1016/j.pharmthera.2019.107453

- Russell, S., Bennett, J., Wellman, J. A., Chung, D. C., Yu, Z. F., Tillman, A., Wittes, J., Pappas, J., Elci, O., McCague, S., Cross, D., Marshall, K. A., Walshire, J., Kehoe, T. L., Reichert, H., Davis, M., Raffini, L., George, L. A., Hudson, F. P., Dingfield, L., … Maguire, A. M. (2017). **Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial**. Lancet (London, England), 390(10097), 849–860. https://doi.org/10.1016/S0140-6736(17)31868-8
- Ziccardi, L., Cordeddu, V., Gaddini, L., Matteucci, A., Parravano, M., Malchiodi-Albedi, F., & Varano, M. (2019). **Gene Therapy in Retinal Dystrophies**. International journal of molecular sciences, 20(22), 5722. https://doi.org/10.3390/ijms20225722
- Maguire, A. M., Russell, S., Wellman, J. A., Chung, D. C., Yu, Z. F., Tillman, A., Wittes, J., Pappas, J., Elci, O., Marshall, K. A., McCague, S., Reichert, H., Davis, M., Simonelli, F., Leroy, B. P., Wright, J. F., High, K. A., & Bennett, J. (2019**). Efficacy, Safety, and Durability of Voretigene Neparvovec-rzyl in RPE65 Mutation-Associated Inherited Retinal Dystrophy: Results of Phase 1 and 3 Trials**. Ophthalmology, 126(9), 1273–1285. https://doi.org/10.1016/j.ophtha.2019.06.017
- Cehajic Kapetanovic, J., Barnard, A. R., & MacLaren, R. E. (2019). Molecular Therapies for Choroideremia. Genes, 10(10), 738. https://doi.org/10.3390/genes10100738
- Patel, U., Boucher, M., de Léséleuc, L., & Visintini, S. (2018). **Voretigene Neparvovec: An Emerging Gene Therapy for the Treatment of Inherited Blindness**. In CADTH Issues in Emerging Health Technologies. (pp. 1–11). Canadian Agency for Drugs and Technologies in Health.

- Doostparast Torshizi, A., & Wang, K. (2018). **Next-generation sequencing in drug development: target identification and genetically stratified clinical trials**. Drug discovery today, 23(10), 1776–1783. https://doi.org/10.1016/j.drudis.2018.05.015
- Ducloyer, J. B., Le Meur, G., Cronin, T., Adjali, O., & Weber, M. (2020). La thérapie génique des rétinites pigmentaires héréditaires **[Gene therapy for retinitis pigmentosa**]. Medecine sciences: M/S, 36(6-7), 607–615. https://doi.org/10.1051/medsci/2020095
- Casey, G. A., Papp, K. M., & MacDonald, I. M. (2020). **Ocular Gene Therapy with Adeno-associated Virus Vectors: Current Outlook for Patients and Researchers**. Journal of ophthalmic & vision research, 15(3), 396–399. https://doi.org/10.18502/jovr.v15i3.7457