Product: ZOLGENSMA

Proper Name: onasemnogene abeparvovec-xioi

Manufacturer: AveXis, Inc

Indication: For the treatment of pediatric patients less than 2 years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the *survival motor neuron 1 (SMN1)* gene.

Description: ZOLGENSMA is a suspension of an adeno-associated viral vector-based gene therapy for intravenous infusion. It is a recombinant self-complementary AAV9 containing a transgene encoding the human survival motor neuron (SMN) protein, under the control of a cytomegalovirus enhancer/chicken-β-actin hybrid promoter.

BLA: 125694

FDA Regulatory Milestone:

DATE	MILESTONES
12/20/2011	PreIND meeting
8/8/2013	IND submission
9/27/2013	Fast Track designation granted
9/30/2014	Orphan Drug designation granted
7/15/2016	Breakthrough Therapy designation granted
6/14/2018	Pre-BLA meeting
8/21/2018	Rare Pediatric Disease designation granted
10/1/2018	BLA 125694 submission
11/28/2018	BLA filed, priority review
2/6/2019	120-day safety and efficacy update received

4/30/2019	Additional efficacy and safety update for the ongoing Phase 3 trial received
6/1/2019	PDUFA* Action Due Date

*PDUFA=Prescription Drug User Fee Act

PDUFA Goal Date: May 31, 2019

FDA Approval Date: May 24, 2019

EU approval: May 18, 2020

Health Canada approval: December 16, 2020

Japan approval: March 19, 2020

Package Insert: Package Insert - ZOLGENSMA

Summary Basis for Regulatory Approval: May 24, 2019 Summary Basis for Regulatory Action - ZOLGENSMA

European Public Assessment Report: May 27, 2020 Assessment Report - ZOLGENSMA

Manufacturing Platform:

PARAMETER	DATA	REFERENCE
Manufacturer	AveXis, Inc	
Transgene	survival motor neuron gene (SMN1)	1
Indication	For the treatment of pediatric patients less than 2 years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene.	3

Virus and Serotype	AAV serotype 9 (AAV9)	2
Cell Substrate	human embryonic kidney cells (HEK293)	3
Manufacturing platform	Plasmid triple transfection	3
Dose in vial/final container	2.0 10e13 vector genomes / mL	1
Dose / patient	1.1 10e13 vector genomes / kg	1

1. Package insert: Package Insert - ZOLGENSMA
2. EPAR full: Zolgensma : EPAR - Public assessment report
3. EPAR quality: Zolgensma : EPAR - Public assessment report (page 14)
4. FDA SBAR – quality: Summary Basis for Regulatory Action - ZOLGENSMA

Advisory Committee:

No advisory committee meeting was held because initial review of information submitted in the BLA did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

Safety:

The major serious risks associated with ZOLGENSMA infusion include acute serious liver injury and substantial increases in aminotransferases. These risks can be mitigated by routine medical management, appropriate labeling of Prescribing Information (PI), and the post-marketing plan proposed by the applicant. Based on review of available data, the safety concerns from the Phase 1 and Phase 3 clinical trials can be monitored through routine medical practice, adequate Prescribing Information, and the voluntary post-marketing plans proposed by the applicant. The

safety data do not indicate the need for a Risk Evaluation and Mitigation Strategy (REMS), a safety post-marketing requirement (PMR) study, or a safety post-marketing commitment (PMC) study.

Clinical Trials:

NCT	TRIAL PHASE	SUBJECTS ENROLLED	TITLE	COUNTRIES
Completed Phase 1 trial				
NCT03421977	1	13	Long-term follow-up study for patients from AVXS-101-CL-101	United States
Ongoing trials				
NCT03306277	3	22	Gene replacement therapy clinical trial for participants with spinal muscular atrophy type 1	United States
NCT03505099	3	30	Pre-symptomatic study of intravenous onasemnogene abeparvovec-xioi in Spinal Muscular Atrophy (SMA) for patients with multiple copies of SMN2	United States, Italy, Australia, Belgium, Israel, Japan, Spain, Canada, Taiwan, Germany, Korea, Republic of, United Kingdom
NCT03461289	3	33	Single-dose gene replacement therapy clinical trial for patients with spinal muscular atrophy type 1	Belgium, France, Italy, United Kingdom

EudraCT Numbers:

- 2020-003678-28
- 2020-000095-38
- 2020-001235-27

Publications:

- Lowes, L. P., Alfano, L. N., Arnold, W. D., Shell, R., Prior, T. W., McColly, M., Lehman, K. J., Church, K., Sproule, D. M., Nagendran, S., Menier, M., Feltner, D. E., Wells, C., Kissel, J. T., Al-Zaidy, S., & Mendell, J. (2019). Impact of Age and Motor Function in a Phase 1/2A

Study of Infants With SMA Type 1 Receiving Single-Dose Gene Replacement Therapy. Pediatric neurology, 98, 39–45. https://doi.org/10.1016/j.pediatrneurol.2019.05.005

- Prior, T. W., Leach, M. E., & Finanger, E. (2000). Spinal Muscular Atrophy. In M. P. Adam (Eds.) et. al., GeneReviews®. University of Washington, Seattle.
- Onasemnogene Abeparvovec. (2020). In LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. National Institute of Diabetes and Digestive and Kidney Diseases.
- Waldrop, M. A., & Kolb, S. J. (2019). Current Treatment Options in Neurology-SMA Therapeutics. Current treatment options in neurology, 21(6), 25. https://doi.org/10.1007/s11940-019-0568-z
- Cappella, M., Ciotti, C., Cohen-Tannoudji, M., & Biferi, M. G. (2019). Gene Therapy for ALS-A Perspective. International journal of molecular sciences, 20(18), 4388. https://doi.org/10.3390/ijms20184388
- Yeo, C., & Darras, B. T. (2020). Overturning the Paradigm of Spinal Muscular Atrophy as Just a Motor Neuron Disease. Pediatric neurology, 109, 12–19. https://doi.org/10.1016/j.pediatrneurol.2020.01.003
- Ziegler, A., Wilichowski, E., Schara, U., Hahn, A., Müller-Felber, W., Johannsen, J., von der Hagen, M., von Moers, A., Stoltenburg, C., Saffari, A., Walter, M. C., Husain, R. A., Pechmann, A., Köhler, C., Horber, V., Schwartz, O., & Kirschner, J. (2020). Handlungsempfehlungen zur Gentherapie der spinalen Muskelatrophie mit Onasemnogene Abeparvovec – AVXS-101 : Konsensuspapier der deutschen Vertretung der Gesellschaft für Neuropädiatrie (GNP) und der deutschen Behandlungszentren unter Mitwirkung des Medizinisch-Wissenschaftlichen Beirates der Deutschen Gesellschaft für Muskelkranke (DGM) e. V [Recommendations for gene therapy of spinal muscular atrophy with onasemnogene abeparvovec-AVXS-101 : Consensus paper of the German representatives of the Society for Pediatric Neurology (GNP) and the German treatment centers with collaboration of the medical scientific advisory board of the German Society for Muscular Diseases (DGM)]. Der Nervenarzt, 91(6), 518–529. https://doi.org/10.1007/s00115-020-00919-8