REGULATIONS AND SCIENCE: COMMON SENSE APPROACHES TO ACCELERATING PATIENT ACCESS TO NOVEL GENE AND CELL THERAPIES

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New products plus predicate data equals faster product development for cell and gene therapies. Informatics related to Clinical Trial and Marketing Applications is an emerging, often overlooked tool in product development that can be used by all sponsors - academic, industry, non-profit to accelerate gene and cell therapy therapeutic interventions. In 2019 FDA anticipated that by 2020 it would be receiving more than 200 INDs per year and by 2025 would be approving 10 to 20 cell and gene therapy products a year based on an assessment of the current pipeline and the clinical success rates of these products (1). The use of converging technologies for different gene and cell therapy indications is an unprecedented opportunity for leveraging predicate data for clinical trial initiation and product licensure. Robust compilation of evidence-based data for safety, efficacy and quality facilitates patient access to therapeutic interventions. Sponsors that are not aware of predicate CMC, clinical and non-clinical data are at risk of performing unnecessary development activities, delay in timelines for concept to IND/CTA to BLA/MAA submission, inefficient use of sponsor and health authority resources and, most importantly, delay of patient access to new medicines. Example questions that can be readily addressed for most programs, by any SME in an organization include: How many trials were conducted to license product X, what country was the phase 1 trial conducted in, what cell line was the product manufactured in, what is the dosage form, what is the final container, what is the storage condition for drug product, how long can it be stored, what changes were made to the product during development, which changes required additional non-clinical or clinical studies? Strategies for compiling what is known and not known in the public domain for gene and cell therapies are available and accessible but may be underutilized due to lack of awareness of the databases and regulatory repositories available on the internet. Both the US and European regulatory agencies (FDA and EMA) provide public information on most aspects of the approval process for Gene Therapy, Cell Therapy and Vaccines in their public assessment reports (EPAR) in Europe and SBAR in the US. Relevant details on the Phase 1, 2 and 3 clinical studies including the number of subjects and endpoints, a description of the manufacturing process, and the animal studies (safety, bio-distribution and efficacy) are listed for each product with redaction of proprietary details. Issues encountered during product development, risks highlighted during the marketing application review, and commitments between the manufacturer-sponsor and the health authority are highlighted. Transcripts of advisory committee meetings where product risks are discussed with experts, the sponsor/manufacturer, and the health authority are provided in the US and provide rationales for reviewer concerns and thought processes during product application review. These health authority repositories complement the international clinical trial databases, company investor reports for public traded companies, grant agency repositories, and the growing number of scientific literature databases available through the internet.

Footnote 1: Statement from FDA Commissioner Scott Gottlieb, M.D. and Peter Marks, M.D., Ph.D., Director of the Center for Biologics Evaluation and Research on new policies to advance development of safe and effective cell and gene therapies (January 2019).

US FDA

Summary Basis of Regulatory Approval:
https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products
- 9 Gene Therapy portfolios
- 12 Cell Therapy portfolios

Product Labeling:
- Patient and Physician Information Leaflets (package inserts) for all approved products

Advisory Committee Meeting Information:
https://www.fda.gov/advisory-committees/cellular-tissue-and-gene-therapies-advisory-committee/meeting-materials-cellular-tissue-and-gene-therapies-advisory-committee
- Agendas and FDA-Sponsor-External Expert presentations (not redacted) with word-for-word transcripts of the meeting discussion

Clinical Trial Information:
https://clinicaltrials.gov/
- >4000 Gene Therapy Trial synopses; >800 active intervention trials, > 300 completed or active Phase 3 studies, >100 Long Term Follow up Studies
- 265 AAV studies; 148 active-recruiting, 84 completed/terminated

EU EMA

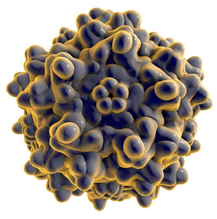
European Public Assessment Report:
https://www.ema.europa.eu/en/medicines/field_ema_web_categories%25253Aname_field/Human/ema_group_types/ema_medicine

Clinical Trial Information:
https://www.clinicaltrialsregister.eu/ctr-search/search

Other Countries

Clinical Trial Registries:

- **Australia:** Australian New Zealand Clinical Trials Registry (ANZCTR)
  https://anzctr.org.au/TrialSearch.aspx
- **Health Canada:** Clinical trial search
  https://health-products.canada.ca/ctdb-bdec/index-eng.jsp
- **India:** Clinical Trials Registry - India (CTRI)
  http://ctri.nic.in/Clinicaltrials/advancesearchmain.php
- **Japan:** UMIN Clinical Trials Registry (UMIN-CTR)
  https://www.umin.ac.jp/ctr/
- **WHO**: International Clinical Trials Registry Platform (ICTRP)
  https://apps.who.int/ictrpws/



CMC

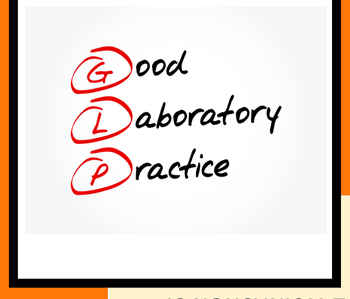
Package Insert: ZOLGENSMA

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.

Manufacturing Process

PARAMETER	DATA
Manufacturer	AveXis, Inc
Transgene	survival motor neuron gene (SMN1)
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.
Virus and Serotype	AAV serotype 9 (AAV9)
Cell Substrate	human embryonic kidney cells (HEK293)
Manufacturing platform	Plasmid triple transfection
Dose in vial/final container	2.0 10e13 vector genomes / mL
Dose / patient	1.1 10e13 vector genomes / kg

References:
- Package insert: Zolgensma
- EPAR: Zolgensma
- FDA SBAR: Summary Basis for Regulatory Action - ZOLGENSMA



Nonclinical

13 NONCLINICAL TOXICOLOGY (Zolgensma)

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility No animal studies have been performed to evaluate the effects of ZOLGENSMA on carcinogenesis, mutagenesis or impairment of fertility.

13.2 Animal Toxicology and/or Pharmacology In toxicology studies conducted in neonatal mice, dose-dependent cardiac and hepatic toxicities were observed following intravenous administration of ZOLGENSMA. ZOLGENSMA-related findings in the myocardium, at doses of 7.9 × 1013 vg/kg and higher, included slight to mild mononuclear cell inflammation accompanied by edema, slight to mild fibrosis, and scattered myocardial cell degeneration/regeneration. Additional cardiac findings at dose levels of 1.5 × 1014 vg/kg and higher included minimal to moderate atrial thrombosis and slight to marked atrial dilation. Liver findings included hepatocellular hypertrophy, Kupffer cell activation, perinuclear vacuolation, and scattered hepatocellular necrosis. Target organ toxicity in the heart and liver was associated with mortality at dose levels of 2.4 × 1014 vg/kg and above, approximately 2.2-fold higher than the recommended clinical dose level.

Various vector products used in the nonclinical development program forLUXTURNA™

Vector	Promoter	Intron	Transgene	PolyA	Description
AAV2-hRPE65	Chicken betaactin (CbA)	CbA exon 1 and intron 1	Human RPE65	Bovine bGH)	Original vector encoding human RPE65
AAV2-cRPE65	CbA	CbA exon 1 and intron 1	Canine RPE65	bGH	Original vector encoding canine RPE65
AAV2-hRPE65v1	CbA	CbA exon 1 and intron 1	Human RPE65	bGH	Stuffer insertion; Splice acceptor mutation
AAV2-hRPE65v2 (LUXTURNA™)	CbA	CbA exon 1 and intron 1	Human RPE65	bGH	Stuffer insertion; Splice acceptor mutation corrected;Kozak sequence;

Clinical

Package Insert: LUXTURNA

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

Regulatory Process

Date	Milestones
	IND
9/20/2005	Pre-IND meeting
6/14/2007	IND 13408 submission by sponsor of Children's Hospital of Philadelphia
12/18/2008	End of Phase 1 type B meeting to discuss a Phase 3 design
3/25/2016	Pre-BLA meeting to discuss a rolling BLA submission and priority review status
2/21/2017	BLA rolling submission part 2: Clinical information
12/19/2017	FDA Approval

Clinical Trials

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

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