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THE BIOMARKER BREAKTHROUGH:

Sarepta's Path to Approval via Surrogate Endpoint Signals a Positive Outlook for Gene Therapy Developers

AUTHORS

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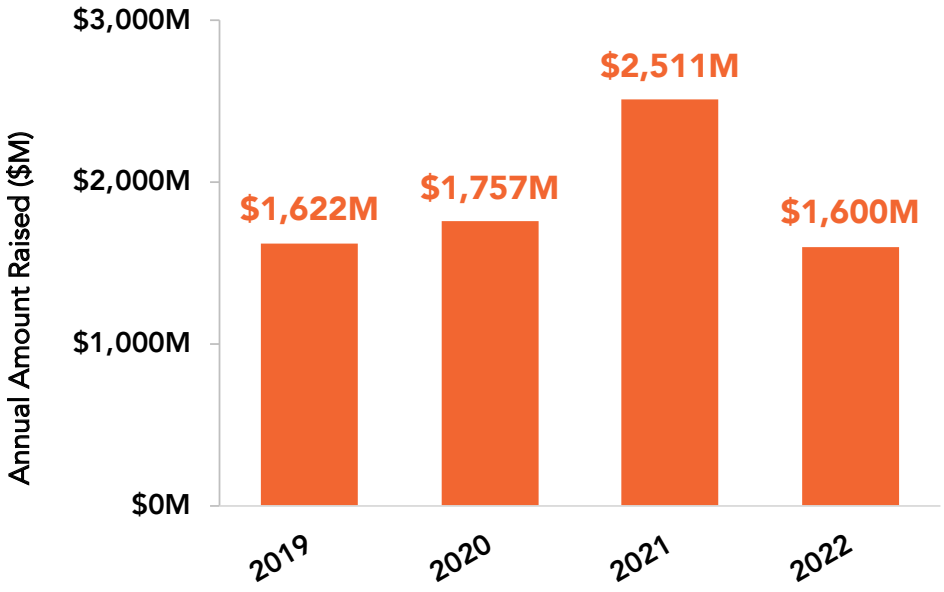
Enthusiasm for gene therapies appears to have slowed in recent years, as demonstrated by organizations including Pfizer[1], Novartis[2,3], and Biogen[3] offloading internal programs or separating from partnership deals related to gene therapies. Gene therapy investment similarly saw a downturn in the last couple of years, with investments returning to pre-pandemic levels[4]. Despite these trends, positive news from the past two months may suggest a ray of hope for gene therapy developers.

On June 22nd, 2023, the FDA granted accelerated approval for Sarepta's Elevidys (delandistrogene moxeparvovec), an adeno-associated virus-based gene therapy, for the treatment of Duchenne Muscular Dystrophy in pediatric patients aged 4 through 5 years.

Figure 1.



US Gene Therapy Venture Financing (2019-2022). US Gene therapy venture financing increased in 2021, but decreased by ~40% in 2022.

Since 2016, ~20 drugs have been granted accelerated approval for indications outside of cancer and infectious disease, including other DMD programs from Sarepta, as well as the other recent gene therapy program, Skysona from Bluebird Bio[6]. While this is not the first accelerated approval for a gene therapy product, or for Sarepta, this accelerated approval is the most recent news which may provide positive signals for the broader gene therapy field.

Table 1.

Manufacturer	Product	Indication	Accelerated Approval Date	Biomarker Approval Endpoint
SAREPTA	**Elevidys**	Duchenne Muscular Dystrophy	6/2023	Microdystrophin
TRAVERE	**Filspari**	Primary Immunoglobulin A Nephropathy (IgAN)	2/2023	Proteinuria
Eisai Biogen	**Leqembi**	Alzheimer's Disease	1/2023	Amyloid Beta Plaque
bluebirdbio	**Skysona**	Cerebral Adrenoleukodystrophy	9/2022	*N/A:* MFD-free Survival
sobi	**Vonjo**	Myelofibrosis	2/2022	*N/A:* Spleen Volume Reduction
calliditas	**Tarpeyo**	Primary Immunoglobulin A Nephropathy (IgAN)	12/2021	Urine Protein-to-Creatinine Ratio
BIOMARIN	**Voxzogo**	Achondroplasia	11/2021	*N/A:* Annualized Growth Velocity
Biogen	**Aduhelm**	Alzheimer's Disease	6/2021	Amyloid Beta Plaque
SAREPTA	**Amondys 45**	Duchenne Muscular Dystrophy	2/2021	Dystrophin

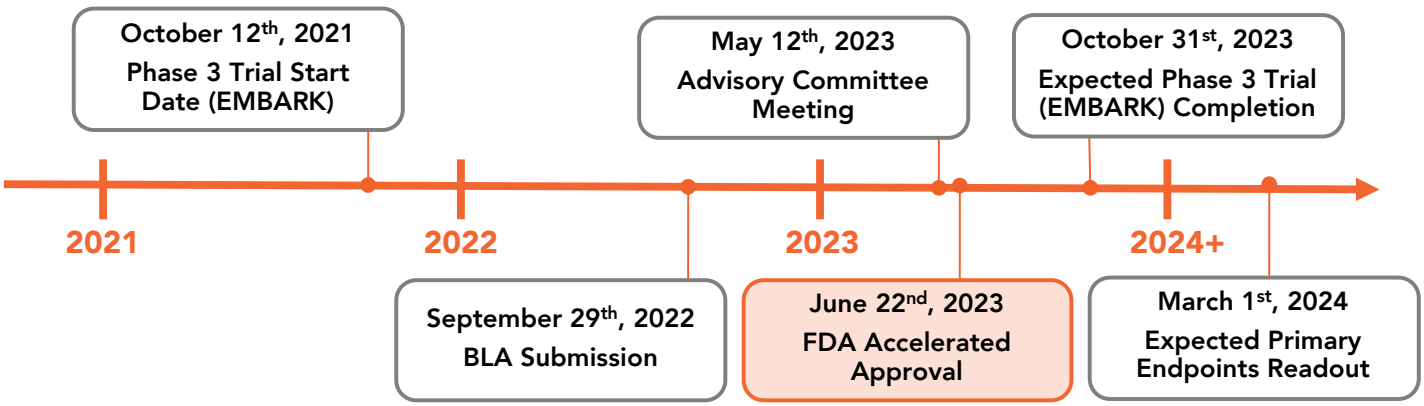
List of Products Granted Accelerated Approval (Since 2021, non-oncology, non-infectious disease). Since 2021, 9 products have been granted accelerated approval, including 5 indicated for Duchenne Muscular Dystrophy (DMD). Two Sarepta programs for DMD were similarly granted accelerated approval prior to 2021. Elevidys is the first gene therapy to receive accelerated approval using a surrogate biomarker endpoint. (🧬) Gene Therapy

This decision comes after a May 12th advisory committee meeting with experts from the Cellular, Tissue, and Gene Therapies Advisory Committee in which the panel voted in favor of accelerated approval of the program. Sarepta pursued accelerated approval using improvement in a biomarker, micro-dystrophin, as a surrogate endpoint for functional improvement. Due to this approach, the FDA required the advisory committee to assess the risk-benefit profile of the therapeutic and determine whether they viewed the surrogate biomarker improvement warranted accelerated approval. The biomarker was deemed to be sufficiently correlated to an increase from baseline in functional skills using the North Star Ambulatory Assessment (NSAA), and ultimately led to accelerated approval.

The decisions by both the advisory committee and the FDA reinforce the rhetoric from the proposed Operation Warp Speed for Rare Diseases that biomarkers may serve as sufficient surrogate endpoints to warrant accelerated approvals, particularly in cases where the biomarker has been correlated with functional endpoints[7].

The advisory committee's recommendation to allow accelerated approval and subsequent FDA decision may provide a potential spark for gene therapy investment and development, as it indicates an opportunity for shortened development timelines and increased acceptance of non-functional endpoints. The news of Sarepta's accelerated approval success, paired with other recent regulatory activity, may result in a return in investment volume to the gene therapy field, particularly for programs leveraging disease-relevant biomarkers in their clinical trial design.

Figure 2.



Streamlined Development Timeline for Sarepta's Elevidys. Sarepta's accelerated approval of Elevidys was granted approximately two years after its Phase 3 trial start date.

The current development pipeline for gene therapies features at least ten other mid-to-late-stage programs that include disease biomarkers as either primary or secondary endpoints[8], though pursuing accelerated approval may not be similarly applicable to all programs. For example, Pfizer's and Helixmith's programs have already begun pivotal phase III trials with Pfizer's DMD results expected in 2024[9], and the companies have not indicated whether it will pursue the accelerated pathway. Moreover, Pfizer's Hemophilia programs will also likely not pursue accelerated approval, given the precedent for the full approval pathway followed by CSL Behring's and BioMarin's gene therapies for Hemophilia B and A, respectively. Lastly, based on FDA data, accelerated approval is typically reserved for rare diseases, and has not been granted to ocular conditions, like age-related macular degeneration, and may pose a challenge for REGENXBIO if they were to consider a similar approach to Sarepta.

Table 2.

Illustrative, Not Exhaustive

Clinical Phase	Asset / Program	Manufacturer	Indication	Biomarker	Endpoint Inclusion
III	fordadistrogene movaparvovec	Pfizer	Duchene Muscular Dystrophy	Mini Dystrophin, Cardiac Troponin	Primary
	giroctocogene fitelparvovec		Hemophilia A	FVII activity	Secondary
	fidanacogene elaparvovec		Hemophilia B	FIX activity	Secondary
	donaperminogene seltoplasmid	HELIXMITH	Diabetic Peripheral Neuropathy	TNF-alpha, IL-1b, IFNy, IL-6,4,10,12p70 cytokines	Secondary
II	RGX-314	REGENXBIO	Age-Related Macular Degeneration	RGX-314 target protein in aqueous humor	Primary
	GT-005	GYROSCOPE A Novartis Company	Geographic Atrophy	Complement Factor I protein expression (*local & systemic*)	Secondary
I / II	**AT-845**	astellas	**Pompe Disease**	**GAA Protein**	**Primary**
	4D-710	4DMT	**Cystic Fibrosis**	**microCFTR Transgene Protein**	**Secondary**

Select Gene Therapy Programs Including Biomarker Endpoints. Biomarkers are included as primary or secondary endpoints for several gene therapy programs, potentially enabling similar pursuit of accelerated approval pathways using surrogate biomarker endpoint data. (**Note:** Gray text represents assets that may not likely pursue or achieve accelerated approval).

Earlier stage gene therapy programs for degenerative conditions may ultimately be better poised to pursue similar pathways to accelerated approval. Examples of phase I/II programs which have included biomarkers as trial endpoints and could feasibly consider accelerated approval pathways include Astellas Gene Therapies' program for Pompe Disease and 4D Molecular Therapeutics' program for Cystic Fibrosis. *(Note: above table is not exhaustive)*

For biopharma developers, this news may serve as an indicator for future opportunities within the gene therapy field. A key consideration to capitalize on this opportunity will be inclusion of biomarker endpoints in clinical trial design, particularly for programs in disease areas with measurable biomarkers and a high unmet need. The FDA's decision to initially restrict the approved patient population, however, may underscore the importance of correlating biomarker expression with functional outcomes and conducting confirmatory / extension studies to reinforce that connection.

Outside of this recent approval news, other recent regulatory initiatives aimed to accommodate faster, more efficient development of complex therapeutics may function as tailwinds for the development of cell and gene therapies. This regulatory activity, and the potential benefit to manufacturers will be explored further in our upcoming white paper: *The Race for Innovation: Regulatory Initiatives to Bolster Cell and Gene Therapy Development.*

References

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[5] Sarepta Therapeutics (Jun. 2023) Sarepta Therapeutics Announces FDA Approval of ELEVIDYS, the First Gene Therapy to Treat Duchenne Muscular Dystrophy. Accessed June 2023

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