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Supplementary information

Clinical development success rates for durable cell and gene therapies

In the format provided by the authors and unedited

Data and analysis

We compared the clinical trial success rates and the overall likelihood of approval from the NEWDIGS FoCUS Pipeline Analysis Model (PAM)[1] for durable cell and gene therapies (dCGTs) to published BIO[2] and IQVIA[3] clinical trial success rates for all therapeutic modalities for all therapeutic areas and for therapeutic areas that correspond to some of the dCGT areas of concentration such as oncology.

The PAM model analyzes all dCGT trials reported in ClinicalTrials.gov from 1988 to the end of 2023 and includes products that use or modify DNA or RNA and are intended to provide a durable effect lasting from a single administration. We broadly apply the FDA Center for Biologics Evaluation and Research (CBER) definition for gene therapy products with the further criteria that the products are expected to produce a durable clinical benefit of at least 18 months.[4] Qualifying durable therapies are those falling into the following modalities: (i) gene replacement therapies both in vivo and ex vivo using viral vectors; (ii) T cell receptors (TCRs) and immune cells engineered to incorporate chimeric antigen receptors (CARs), (iii) gene-editing therapies (based on zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENS), and clustered regularly interspaced short palindromic repeats (CRISPR)-associated protein 9 (Cas9)); and (iv) long-acting DNA plasmids. Clinical trials were first identified using therapeutic class and modality search criteria in the PharmaProjects® database[5] and then confirmed using the ClinicalTrials.gov database[6] using a combination of natural language processing and manual searches and extraction. We also identified additional clinical trials solely from ClinicalTrials.gov.

Only active interventional trials with a known status and development phase were included in the database (Phase I, including Phase I/II; Phase II, including Phase II/III; and Phase III trials) with the following statuses: recruiting, active, not recruiting, enrolling by invitation, and completed). In instances where clinical trials investigate multiple potential indications, we tracked and projected each product-indication combination individually. Similarly, we tracked a drug candidate with multiple clinical trials for different indications individually. In cases where concurrent active trials existed for a specific product indication, the highest phase was selected to represent the product indication for the analysis. We excluded clinical trials on ClinicalTrials.gov that were registered by a Chinese developer, with all registered trial sites located in China and with no record of international commercial partners, as we assumed these products were being developed for local markets and are unlikely to be submitted for US FDA approval.

Our dataset comprised all identified qualifying therapies with active clinical trials starting on or before December 31, 2023. Registrations, launches, and complete response letters were also included. We then loaded data from all the identified trials into a macro-containing Excel sheet that parsed data into drug, disease, trial, phase, modality, and the time starting and ending each phase. An Excel macro evaluates every drug indication's start and end dates of each phase, marking if the phase trial is in progress or complete, or if a new phase was started. Success in a phase is when a trial starts a phase, completes that phase, and then moves on to either a new phase or a registration/launch step. Failures are trials with phases that start, complete, and then do not progress to new phases within eleven years or are publicly announced as a discontinued indication or program. We did not consider trials still in progress as either successes or failures, and we did not include them in the denominator until the phase had ended and either moved to progressed or not. For this analysis, we held all data to a cut-off point of December 31, 2023; any progression to a new phase or completion of an existing phase after this cut-off was not counted. It should be noted that given the very small patient populations available for clinical trial inclusion for dCGTs, clinical trial phases are often combined. For example, 67% of orphan gene therapy trials start in Phase I/II. Haematological CAR-Ts start in Phase I/II in 30% of programs. Not all trials progress linearly (e.g., Phase I, Phase II, Phase III, registration, approval). While rare, trials can skip phases and can still be considered successful if they progress to a higher level.

Success rates were calculated for each phase in clinical trial progression by dividing the number of trials progressing to the next clinical trial phase (including submission for NDA or BLA and/or receiving market approval) by the total completed trials for each phase. For example, if there were one hundred Phase I trials with a completed status, we then looked to the next status to determine if the trial progressed to Phase I/II or II. In this example, if thirty-five Phase I trials with a complete status subsequently move to the next phase, we counted them as ‘successes.’ In this example, the Phase I success rate would be 35%. Because developers sometimes stall or otherwise delay trials, we allow up to eleven years from the date of the complete status

before a trial with a complete status is no longer considered to have the potential to move to another phase. We did not include incomplete trials (still active trials with no end date) in our calculation. We calculated Phase II and Phase I/II trial success rates using a simple average. This methodology is the same as that used for the comparison data. Our analysis distinguished success rates for haematological CAR-T/TCR trials from all other gene therapy product trials.

To approximate the overall likelihood of approval (LOA), the composite success rate percentage, we calculated this as Phase I success rate x (average success rate for Phase II + Phase I/II) x (average success rate for Phase III + Phase II/III) x success rate for NDA/BLA Application.

For rare disease gene therapies, the calculation is thus:
55.0% x 49.2% x 68.4% x 100% = 18.5%

For haematological CAR-T/TCR therapies, the LOA calculation is:
26.3% x 38.7% x 75.0% x 100.0% = 7.6%

Our comparative analysis selected the most recent BIO and IQVIA estimates over academic alternatives to ensure comparison to datasets that extended through at least 2020 (Table 1). Literature searches found no published academic research using clinical trial success rates as an endpoint beyond 2019.[7]

Summary of industry and academic references with published clinical drug development success rates estimates

	PAM	BIO	IQVIA	Wong[6]	DiMasi[1]	Yamaguchi[5]
Data Sources	ClinicalTrials.gov	Biomedtracker by Informa Pharma Intelligence	IQVIA Pipeline Intelligence	TrialTrove and PharmaProjects by Citeline	50 biopharma	PharmaProjects
Trial Data Date Range	1988-2023 (35 years)	Jan 2011-Nov 2020 (9.9 years)	2010-2023 (14 years)	2000-2015 (16 years)	1993-2009 (17 years)	2000-June 2019 (18.5 years)

We compared dCGT's likelihood of approval from Phase I and individual clinical development phase success rates to the more general drug pipeline. All sources similarly grouped Phase I/II trials and Phase II/III trials into Phase II and Phase III, respectively, facilitating comparison. BIO also reported estimates by major disease areas, allowing more direct oncology comparisons for the CAR-T/TCR dCGT pipeline.
Our decision to compare LOA and phase success rates to both IQVIA and BIO was driven by the relative advantages of each, recognizing that there is no perfect comparison. IQVIA data has the advantage of having the same cutoff date as our data and is reflective of current market conditions. Although the cutoff date was 2020, the success rates from BIO allow a comparison for all haematologic oncology programs to haematological CAR-T/TCR programs.

dCGT Trial Phase Level Outcomes

			Orphan Gene Therapy	Haematological CAR-T/TCR Therapy
Started			**195**	**402**
Phase 1				
	Active		14	121
	Completed		20	99
		Advanced to subsequent Phase	11	26
		No subsequent Phase	9	73
Phase 1/2				
	Active		76	48
	Completed		45	58
		Advanced to subsequent Phase	22	18
		No subsequent Phase	23	40
Phase 2				
	Active		5	30
	Completed		14	17
		Advanced to subsequent Phase	7	11
		No subsequent Phase	7	6
Phase 3				
	Active		16	7
	Completed		20	4
		Advanced to subsequent Phase	14	3
		No subsequent Phase	6	1
Registration				
	Active		3	2
	Completed		12	10
Approval			12	10
	Full Approval		10	7
	Accelerated Approval (AAP)		2	3
		AAP with subsequent full approval	1	0

dCGT Success Rate Comparison to BIO and IQVIA

	PAM dCGT (1988-2023)		BIO (2011-2020)			IQVIA Source data: (2010-2023)
	Rare Disease Gene Therapy	**Haematological CAR-T/TCR Therapy**	**All therapeutic areas**	**All Oncology**	**Haematological Oncology**	**All Therapeutic Areas**
Phase I	55.0%	26.3%	52.0%	48.8%	50.1%	45%
Phase II + Phase I/II	49.2%	38.7%	28.9%	24.6%	27.8%	36%
Phase III + Phase II/III	68.4%	75.0%	57.8%	47.7%	60.0%	56%
NDA/BLA Application	100.0%	100.0%	90.6%	92.0%	90.0%	81%
Likelihood of Approval (LOA)	18.5%	7.6%	7.9%	5.3%	7.5%	7.3%

[1] Young CM, Quinn C, Trusheim MR. Durable cell and gene therapy potential patient and financial impact: US projections of product approvals, patients treated, and product revenues. *Drug Discovery Today*. 2022;27(1):17-30. doi:10.1016/j.drudis.2021.09.001

[2] Clinical Development Success Rates and Contributing Factors 2011-2020 | BIO. Accessed October 14, 2024. https://www.bio.org/clinical-development-success-rates-and-contributing-factors-2011-2020

[3] Global Trends in R&D 2024: Activity, productivity, and enablers. Accessed October 14, 2024. https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/global-trends-in-r-and-d-2024-activity-productivity-and-enablers

[4] U.S. Food & Drug Administration. Cellular & Gene Therapy Products. FDA. March 20, 2023. Accessed October 14, 2024. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products

[5] Pharmaprojects: the industry standard for tracking and analyzing the global drug R&D landscape. Citeline. Accessed October 14, 2024. https://www.citeline.com/en/products-services/clinical/pharmaprojects

[6] ClinicalTrials.gov. Accessed October 14, 2024. https://clinicaltrials.gov/

[7] Yamaguchi S, Kaneko M, Narukawa M. Approval success rates of drug candidates based on target, action, modality, application, and their combinations. *Clinical and Translational Science*. 2021;14(3):1113-1122. doi:10.1111/cts.12980