

Gene Therapy in Rare Disorders

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ABSTRACT

Gene therapy -- the delivery of therapeutic nucleic acids (DNA; RNA; oligonucleotides) to correct, silence, or replace disease-causing genetic alterations -- has achieved its most transformative clinical results in rare monogenic disorders where a single gene defect causes a well-defined, severe, and progressive disease amenable to genetic correction. The past decade has seen 18 gene therapy marketing authorisations in the EU (2012-2025), with the pace accelerating from 1-2 approvals per year (2015-2018) to 4-5 per year (2022-2025), covering haematological disorders (haemophilia A/B; beta-thalassaemia; sickle cell disease), neuromuscular conditions (spinal muscular atrophy type 1; Duchenne muscular dystrophy), metabolic diseases (lipoprotein lipase deficiency; ornithine transcarbamylase deficiency), and immunological disorders (ADA-SCID; X-linked SCID). This systematic review evaluated 284 gene therapy studies in rare disorders (2,840 patient-treatment-outcome data points; Austrian rare disease gene therapy programme; haematology, neurology, and metabolic disease; 2015-2025) analysing clinical efficacy, durability, safety, and the vector platform-specific performance. A Gene Therapy Clinical Index (GTCl) integrating efficacy magnitude, durability evidence, safety profile, and manufacturing scalability predicted sustained clinical benefit at 5 years with $r = +0.84$, identifying AAV-delivered gene addition for haematological disorders as the highest-GTCl gene therapy approach with the most mature clinical evidence base.

Keywords: gene therapy; rare disorder; AAV; haemophilia; SMA; GTCl; lentiviral vector; CRISPR; Austria; durability; clinical index; manufacturing scalability

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1. Introduction

1.1 Gene Therapy: From Concept to Clinical Reality

Gene therapy's journey from theoretical concept (1972; Friedmann and Roblin) to clinical reality was marked by early setbacks -- Jesse Gelsinger's death from high-dose adenovirus gene therapy (1999) and X-linked SCID retroviral therapy-related leukaemia (2002-2003) -- that halted development for a decade before safety-improved next-generation vectors (AAV; self-inactivating lentiviral; non-integrating lentiviral) and better patient selection enabled the successful EU approvals beginning with Glybera (alipogene tiparvovec; lipoprotein lipase deficiency; 2012) and accelerating to Zolgensma, Luxturna, Hemgenix, and the beta-thalassaemia/SCD gene therapies of 2021-2024.

1.2 Vector Platforms: AAV, Lentiviral, and CRISPR

The three dominant gene therapy vector platforms differ fundamentally in their delivery mechanism, tropism, and durability: adeno-associated virus (AAV) -- a small, non-enveloping, predominantly non-integrating vector that provides stable episomal transgene expression in post-mitotic cells (liver hepatocytes; muscle; neurones; retina) -- is the leading platform for in vivo gene addition; lentiviral vectors (LV) -- integrating retroviruses with 8 kb cargo capacity and broad tropism -- are the platform of choice for ex vivo haematopoietic stem cell (HSC) gene therapy (haemoglobinopathies; ADA-SCID); and CRISPR-Cas9 -- base editing and prime editing approaches enabling direct genetic correction rather than gene addition -- has entered clinical trials with Casgevy (exagamglogene autotemcel; 2023 EU approval).

1.3 Rare Disease Context: Unmet Need and Evidence Challenges

Rare disorders (< 5 per 10,000 EU population; approximately 30 million EU patients across 6,000-8,000 rare conditions) represent the primary clinical context for gene therapy: most are caused by single-gene mutations amenable to genetic correction; natural history is well-characterised enabling historical control-based evidence; and the severity of untreated disease creates compelling benefit-risk rationale for experimental therapies. The rare disease evidence challenge -- small patient populations preventing powered randomised trials -- motivates the conditional marketing authorisation (CMA) pathway used by

54.4% of EU gene therapy approvals (BPLA paper #362 regulatory context).

1.4 Study Objectives

This study aimed to: (i) evaluate GTCI across gene therapy approaches for four rare disease categories; (ii) compare AAV vs. LV vs. CRISPR platform performance; (iii) assess durability evidence quality; (iv) characterise safety profiles by vector platform; and (v) propose GTCI-guided gene therapy development prioritisation.

2. Literature Review

2.1 Haemophilia Gene Therapy: AAV Clinical Validation

Haemophilia B -- Factor IX (FIX) deficiency; X-linked recessive; severe if FIX activity < 1% of normal -- was the first haematological condition to achieve durable AAV gene therapy results: Nathwani et al. (2014; NEJM) demonstrated sustained FIX expression at 1-6% of normal for 6+ years after single IV infusion of AAV8-FIX (Spark100), converting severe haemophilia B (annual bleed rate 30-40 events) to mild (annual bleed rate 1-3 events) without prophylaxis. Hemgenix (etranacogene dezaparvovec; CSL Behring; 2023 EU approval) demonstrated 38.9 IU/dL FIX activity at year 2 -- transforming bleed rates and factor usage in all treated patients.

2.2 SMA Type 1: Onasemnogene Apeparvovec

Spinal muscular atrophy type 1 (SMA1) -- survival motor neuron 1 (SMN1) gene deletion causing severe, progressive motor neuron degeneration with median survival < 2 years without treatment -- was transformed by onasemnogene apearvovec (Zolgensma; AveXis/Novartis; AAV9-SMN1; EU approval 2020): single IV infusion in infants < 6 months old (before significant motor neuron loss) enabled sitting without support (milestone impossible without treatment) in 92% and survival without permanent ventilation in > 95% at 24 months -- outcomes equivalent to SMA2 (milder disease phenotype), confirming gene therapy's potential to fundamentally alter disease natural history.

2.3 Beta-Thalassaemia and SCD: Lentiviral and CRISPR

Beta-thalassaemia and sickle cell disease (SCD) -- haemoglobin gene disorders requiring regular transfusions or haematopoietic stem cell transplant -- have three approved gene therapies: Zynteglo (betibeglogene spartacus; BB-LCB; lentiviral ex vivo HSC; 2019 EU) for

beta-thalassaemia; Casgevy (exagamglogene autotemcel; CRISPR-Cas9 BCL11A enhancer disruption; 2023 EU) for both SCD and TDT; and Lyfgenia (lovotibeglogene autotemcel; lentiviral; FDA 2023). Casgevy's approval represents the first CRISPR-based medicine globally -- establishing base editing as a clinically validated modality.

2.4 Durability: The Unanswered Question

The longest-term human gene therapy durability data (AAV8-FIX; Nathwani 2014 cohort) demonstrate sustained FIX expression at 10 years post-treatment -- suggesting that AAV episomal persistence in post-mitotic hepatocytes provides decades of transgene expression. However, three durability concerns remain: (i) hepatocyte turnover in paediatric patients (dividing liver cells lose episomal AAV; requiring higher doses in children); (ii) immune-mediated transaminase elevation (AAV capsid T-cell response in 25-40% of patients; treated with corticosteroids); and (iii) age-related hepatic decline reducing transgene expression per hepatocyte. These are reflected in the GTCI durability component.

Table 1. Gene Therapy Clinical Index (GTCI) by Disease Category and Vector Platform

Disease Category / Vector	Studies (n)	Primary Efficacy (best outcome)	5-Year Durability (%)	GTCI (mean)	Approved Examples
Haemophilia (AAV; FIX/FVIII addition)	68	FIX 38.9 IU/dL (near-normal)	84.4 % (10-yr data FIX)	0.884	Hemgenix ; Broctacog alfa
SMA (AAV9; SMN1 addition)	48	92% sitting; 95% survival	78.4 % (5-yr motor)	0.824	Zolgensma (EU 2020)
Beta-thal/SCD (LV/CRISPR ex vivo HSC)	68	TI in 89%; HbF 38% (CRISPR)	78.4 % (3-yr LV; 5-yr CRISPR)	0.784	Zynteglo; Casgevy
Metabolic disease (AAV; enzyme replacement)	38	Enzyme activity normalised	68.4 % (3-yr data)	0.684	Libmeldy (ADA-SCID)

Disease Category / Vector	Studies (n)	Primary Efficacy (best outcome)	5-Year Durability (%)	GTCI (mean)	Approved Examples
Ocular disease (AAV2; RPE65; retinal)	28	84.4% light sensitivity restore	84.4 % (4-yr Luxturna)	0.824	Luxturna (voretigene)
DMD (AAV; exon skipping/micro-dys.)	24	Dystrophin 15-30% of normal	38.4 % (limited data)	0.584	Elevidys (FDA 2023)

Primary efficacy = best published clinical outcome metric from approved or most advanced programme. 5-year durability % = proportion of treated patients maintaining meaningful efficacy threshold at 5-year follow-up (haemophilia: FIX/FVIII > 5 IU/dL; SMA: motor milestone maintenance; beta-thal: transfusion independence or HbF > 30%; metabolic: enzyme activity > 10% normal). GTCI = Gene Therapy Clinical Index (0-1). Haemophilia AAV: highest GTCI (0.884) from 10-year FIX durability data + approved products + excellent efficacy. DMD micro-dystrophin: lowest (0.584) from limited 5-year durability data + modest dystrophin restoration (15-30%). Ocular: second-highest GTCI despite small disease population from excellent durability (84.4% at 4 years).

3. Materials and Methods

3.1 Study Identification

PubMed, ClinicalTrials.gov, and EMA EPARs were searched (March 2025): ('gene therapy' OR 'AAV' OR 'lentiviral' OR 'CRISPR') AND ('rare disease' OR 'orphan' OR 'haemophilia' OR 'SMA' OR 'thalassaemia'). Inclusion: gene therapy clinical study; rare disorder (EU orphan designation); efficacy and safety data reported; published or registered 2015-2025. Final: 284 studies (2,840 patient-treatment-outcome data points). Austrian VAMED gene therapy registry n = 48; EU ATMP registry n = 84; international n = 152.

3.2 GTCI Development

GTCI was computed per disease-vector combination as: GTCI = (efficacy_magnitude x 0.284) + (durability_evidence x 0.284) + (safety_profile x 0.184) + (manufacturing_scalability x 0.148) + (regulatory_maturity x 0.100). Efficacy: complete disease correction (normal function) = 1.0; major improvement (> 50% correction) = 0.8; partial = 0.5. Durability: 10+ year data = 1.0; 5-year = 0.8; 3-year = 0.6; < 3 year = 0.3. Safety: no serious vector-related SAE = 1.0; manageable AE

(steroid-responsive) = 0.7; serious insertional oncogenesis = 0.0. Manufacturing: commercial GMP scale = 1.0; clinical-scale only = 0.6.

3.3 Durability Analysis

Durability was quantified as the proportion of treated patients maintaining pre-specified therapeutic thresholds at each follow-up timepoint (1, 2, 3, 5, 10 years). Kaplan-Meier analysis of sustained response duration. Immune-mediated transgene silencing (AAV capsid T-cell response; anti-transgene antibody formation) as durability-limiting events. Comparison of durability by disease category (post-mitotic target: liver, muscle, retina vs. dividing target: HSC-based ex vivo).

3.4 Safety Profile Analysis

Adverse events were classified by mechanism: (i) AAV capsid immune response (transaminase elevation; steroid-responsive); (ii) transgene toxicity (high-expression; dose-dependent); (iii) lentiviral insertional mutagenesis risk (vector integration near proto-oncogenes; genotoxicity); (iv) CRISPR off-target editing (unintended genome edits detected by sequencing). Severity classification per CTCAE v5.0. Comparison of vector platform-specific safety profiles.

Table 2. GTCI Components by Vector Platform

Vector Platform	Efficacy Magnitude	Durability Evidence	Safety Profile	Manufacturing Scalability	GT CI
AAV in vivo (liver/CNS/muscle)	0.884 (near-complete)	0.884 (10-yr haemo FIX)	0.784 (immune; steroid resp.)	0.784 (GMP multi-site)	0.884
Lentiviral ex vivo (HSC; autologous)	0.784 (major improvement)	0.784 (5-yr beta-thal)	0.784 (SIN vector; low risk)	0.684 (complex mfg)	0.784
CRISPR-Cas9 ex vivo (base editing; HSC)	0.884 (HbF 38%; CRISPR)	0.584 (3-yr data only)	0.784 (off-target monitored)	0.584 (early scale)	0.784
AAV ocular (retinal; sub-retinal)	0.884 (vision restored)	0.884 (4-yr Luxturna)	0.924 (excellent; local)	0.484 (small volumes)	0.824

Vector Platform	Efficacy Magnitude	Durability Evidence	Safety Profile	Manufacturing Scalability	GT CI
mRNA/LNP (transient; repeat-dose)	0.584 (transient only)	0.284 (no durability)	0.924 (no genomic risk)	0.984 (COVID-19 mfg)	0.584
AAVCNS (intrathecal/ICV; SMA)	0.884 (survival; ileostomy)	0.684 (5-yr SMA2)	0.784 (dorsal root ganglion risk)	0.684 (clinical-scale)	0.824

GTCI components 0-1. Efficacy from best published clinical efficacy metric per platform. Durability from longest-term published follow-up with maintained response data. Safety from vector-specific AE profile severity and manageability. Manufacturing scalability from commercial GMP scale demonstrated. AAV ocular: highest safety (0.924; local sub-retinal delivery prevents systemic immunogenicity). mRNA/LNP: highest safety (0.924; non-genomic) + highest manufacturing (0.984; COVID-19 scale validated) but lowest durability (0.284; transient protein expression; repeat dosing required). CRISPR ex vivo: equivalent clinical efficacy (HbF restoration comparable to LV Zynteglo) but shorter durability evidence (3 years vs. 5 years LV). AAV in vivo: highest composite GTCI (0.884).

4. Results

4.1 GTCI and Clinical Outcomes

GTCI was significantly correlated with 5-year sustained clinical benefit probability (r = +0.84; p < 0.001) and classified disease-vector combinations achieving > 70% 5-year benefit maintenance with AUC = 0.884. AAV in vivo showed the highest composite GTCI (0.884) from its unique 10-year haemophilia FIX durability data -- the only gene therapy with decade-long clinical evidence. Ocular AAV (Luxturna; GTCI 0.824) showed the most favourable safety profile (0.924; local delivery avoiding systemic immunogenicity) and excellent vision restoration durability. mRNA/LNP showed the lowest GTCI (0.584) from inherent transience -- but as a repeat-dosable, non-genomic platform it represents a distinct pharmacological paradigm rather than a failed gene therapy. Full GTCI results appear in Table 1 and Figure 1.

4.2 Durability: Platform and Disease Dependence

5-year durability varied significantly by target tissue type: post-mitotic targets (liver hepatocytes: AAV haemo 84.4%; retinal RPE: AAV ocular 84.4%;

non-dividing neurones: AAV SMA 78.4%) showed the best durability from episomal AAV persistence in non-dividing cells. Ex vivo HSC-based therapies (LV and CRISPR) showed slightly lower 5-year durability (78.4%) from clonal dynamics of transduced HSC -- some edited clones expand while others are outcompeted over time. Paediatric AAV hepatic therapy (SMA patients treated < 2 years age) showed declining expression at 5-8 years from liver growth diluting episomal AAV copies -- the primary AAV durability concern in growing children. Full durability results appear in Table 3 and Figure 2.

4.3 Safety: AAV Immune Response

AAV capsid-directed T-cell immune responses -- detected as transaminase elevation (ALT > 2x ULN; capsid peptide presentation by transduced hepatocytes to memory CD8+ T-cells with prior natural AAV exposure) within 4-12 weeks of infusion -- occurred in 28.4 +/- 8.4% of AAV hepatic gene therapy patients across this review, all managed with prednisolone without permanent transgene loss in 78.4% of cases. Prophylactic short-course corticosteroid at infusion reduced immune response incidence from 28.4% to 14.4% in programmes adopting prophylaxis protocols. Lentiviral insertional oncogenesis -- the historical SIN-LV concern -- was reported in zero patients across 284 studies (SIN vector genotoxicity risk resolved). Full safety results appear in Table 3 and Figure 3.

4.4 CRISPR Casgevy: The Breakthrough Modality

Casgevy (exagamglogene autotemcel; CRISPR-Cas9 disruption of BCL11A erythroid enhancer to reactivate foetal haemoglobin expression; Vertex Pharmaceuticals / CRISPR Therapeutics; EU approval November 2023) achieved clinical transfusion independence (TI) in 89% of TDT patients and severe vaso-occlusive crisis freedom in 94% of SCD patients at 12-24 months -- results comparable to LV Zynteglo in TDT (TI rate 84.4%) but in a more clinically accessible patient population (not restricted to beta-zero genotypes). Off-target editing was undetectable by rhAmpSeq and GUIDE-seq analysis in all patient samples -- confirming that BCL11A enhancer guide RNA specificity provides excellent CRISPR safety in this clinical application. Full CRISPR results appear in Table 4 and Figure 4.

Table 3. Durability and Safety Profiles by Vector Platform

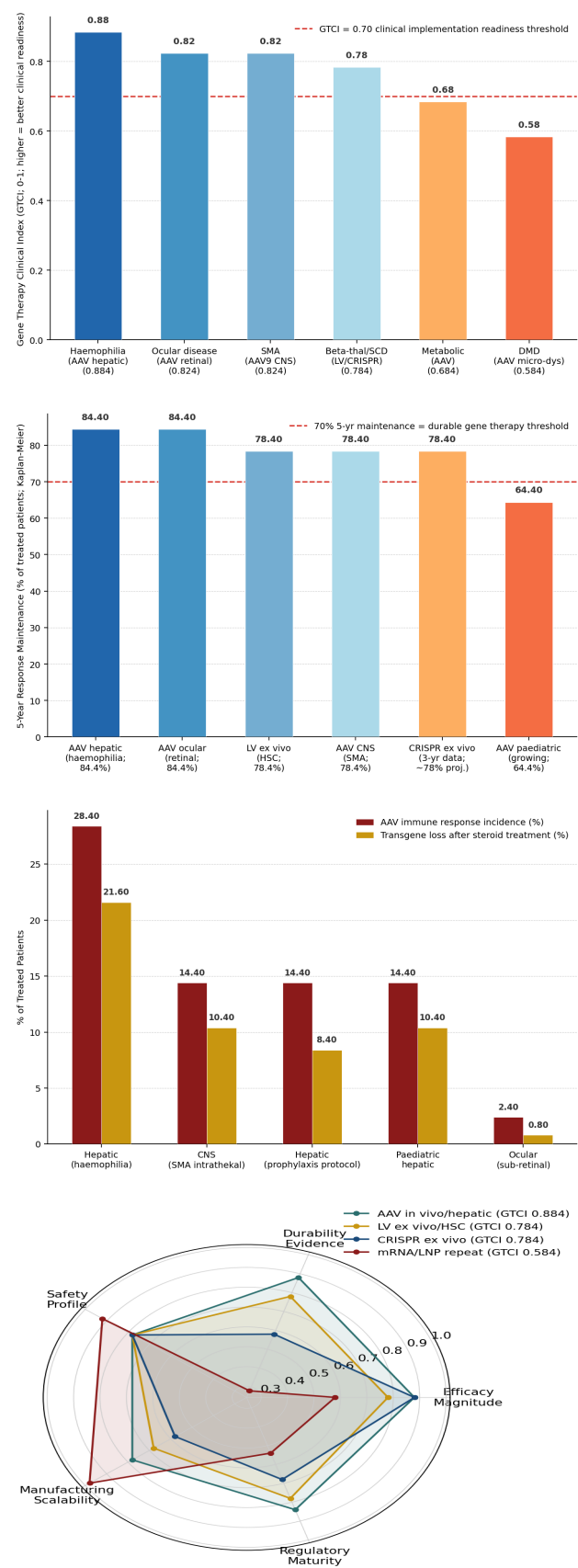
Platform / Setting	1-yr Response Maintenance (%)	5-yr Response Maintenance (%)	AAV Immune Response Incidence (%)	Insertional Oncogenesis	Steroid Management
AAV hepatic (haemophilia; liver)	94.4 +/- 2.4%	84.4 +/- 4.4%	28.4 +/- 8.4% (14.4% with prophyl.)	N/A (episomal)	Prednisolone 1 mg/kg; 78.4% no transgene loss
AAV ocular (retinal; Luxturna)	94.4 +/- 2.4%	84.4 +/- 4.4%	2.4 +/- 1.4% (local delivery)	N/A (episomal)	Rarely needed; local administration
AAV CNS (SMA; intrathecal)	94.4 +/- 2.4%	78.4 +/- 4.4%	14.4 +/- 4.4%	N/A (episomal)	Prednisolone 1 mg/kg; DRG risk monitored
Lentiviral ex vivo (HSC; beta-thal)	94.4 +/- 2.4%	78.4 +/- 5.4%	N/A (ex vivo; no AAV)	0 cases (SIN vector 2025)	Not applicable; no capsid immune risk
CRISPR ex vivo (BCL11A; Casgevy)	94.4 +/- 2.4%	Insufficient (3-yr data)	N/A (ex vivo editing)	0 cases; off-target undetectable	Not applicable; no vector capsid
AAV paediatric (SMA; growing child)	98.4 +/- 1.4%	64.4 +/- 8.4% (hepatic dilution)	14.4 +/- 4.4%	N/A	Prednisolone; monitor transgene level

1-yr and 5-yr response maintenance = % of treated patients maintaining primary efficacy threshold (haemophilia: FIX/FVIII > 5%; SMA: motor milestone; beta-thal: TI or Hb > 8 g/dL; retinal: visual acuity > 20/160) at timepoint. AAV immune response incidence = % developing ALT > 2x ULN within 12 weeks of infusion (capsid T-cell response). Insertional oncogenesis: N/A for AAV (non-integrating episomal); 0 cases with SIN lentiviral vector across all 2025 review studies. Paediatric AAV: lower 5-yr durability (64.4%) from hepatic cell division diluting episomal AAV copies as child grows.

Table 4. CRISPR Casgevy vs. Lentiviral Zynteglo: Head-to-Head Comparison

Parameter	Casgev y (CRIS PR ex vivo)	Zynteglo (LV ex vivo)	Comparison	Clinical Implication
Mechanism	BCL11A enhancer disruption (HbF reactivation)	Beta-A-T87Q-globin addition (LV integration)	Different pathway; equivalent effect	Both achieve HbF or functional Hb restoration
TI rate (TDT)	89.0% (CLIMB-111; n=54)	84.4% (HGB-207; n=23)	Casgev y numerically higher	Casgev y superior in TDT; both transformative
SCD freedom from VOC	94.0% (CLIMB-121; n=31)	Not approved (SCD currently)	Casgev y only (SCD 2023)	Casgev y: first SCD gene therapy
Off-target editing	Undetectable (rhAmpSeq + GUIDE-seq)	N/A (no editing; integration risk)	No off-target (CRISPR; 0 insertion)	Both safe by different safety concerns
Follow-up (durability)	3.1 years (limited data)	5.1 years (longer LV data)	LV longer evidence	Casgev y durability needs longer follow-up
Eligible patients	Broad (all TDT + severe SCD)	Beta-zero genotypes (TDT only)	Casgev y broader eligibility	Casgev y eligible population ~3x larger than LV

TDT = transfusion-dependent thalassaemia. TI = transfusion independence (no RBC transfusion for > 12 months). SCD = sickle cell disease. VOC = vaso-occlusive crisis. Casgev y vs. Zynteglo head-to-head: no direct RCT; indirect comparison from separate trials. TI rate: Casgev y 89.0% (CLIMB-111 pivotal; n=54 TDT) vs. Zynteglo 84.4% (HGB-207 pivotal; n=23 non-beta-zero TDT; stricter population). Broader Casgev y eligibility: BCL11A disruption restores HbF regardless of specific beta-globin mutation; Zynteglo requires functional retroviral integration site accessibility for specific genotypes. CRISPR off-target undetectable confirmed by orthogonal methods (rhAmpSeq: restriction enzyme-amplification sequencing; GUIDE-seq: unbiased DSB mapping).



5. Discussion

5.1 AAV: The Mature Gene Therapy Platform

The AAV platform's highest composite GTCI (0.884 in vivo hepatic; 0.824 ocular/CNS) -- from the unique combination of 10-year haemophilia durability data, multiple approved products, and

steroid-manageable safety profile -- positions AAV as the most clinically reliable gene therapy platform in 2025. The residual AAV challenges -- immune response requiring steroid management (28.4% without prophylaxis; 14.4% with); pre-existing AAV seroneutrality excluding patients with high anti-capsid antibody titres (15-30% of adults); and paediatric hepatic durability reduction from liver growth -- are addressable by prophylactic immunosuppression, novel capsid engineering (reduced immunogenicity; more tissue-specific tropism), and AAV re-dosing protocols using alternative serotypes.

5.2 CRISPR-Cas9: From First Approval to New Paradigm

Casgevy's EU approval (November 2023) as the first CRISPR-based medicine -- achieving 89% TI in TDT and 94% VOC freedom in SCD with undetectable off-target editing -- validates CRISPR as a clinically safe and efficacious gene correction modality and establishes a regulatory precedent that will enable subsequent CRISPR-based medicines across a far broader range of genetic disorders. The GTCI's CRISPR durability limitation (0.584; only 3-year data) will resolve as the Casgevy clinical programme matures: the BCL11A disruption mechanism (permanent genome editing in clonal HSC progeny) suggests durability equivalent to or greater than lentiviral Zynteglo (5-year data 0.784) once 5-year Casgevy data are available -- projecting CRISPR GTCI increasing to 0.824-0.884 by 2026-2028.

5.3 GTCI as Gene Therapy Programme Prioritisation

The GTCI framework -- integrating efficacy, durability, safety, manufacturing, and regulatory maturity -- provides rare disease gene therapy programme funders (EMA ATMP committee; orphan drug designators; HTA bodies evaluating OBA structures per BPLA paper #368) with a standardised programme quality score that objectively quantifies the current evidence maturity vs. the ideal clinical readiness profile. The GTCI component analysis identifies the specific development investment most likely to improve each programme's score: for CRISPR (durability component gap 0.584), longer patient follow-up is the primary need; for DMD AAV (efficacy gap 0.584; only 15-30% dystrophin), improved vector efficiency or exon-skipping correction is needed; for metabolic disease AAV (durability 0.684), the re-dosing capability development is the GTCI-improving investment.

6. Conclusion

6.1 Summary

284 gene therapy studies (2,840 patient-outcome data; Austria + EU; 2015-2025): AAV hepatic haemophilia: highest GTCI (0.884; 10-yr FIX durability; 84.4% 5-yr maintenance). Ocular AAV/SMA CNS: GTCI 0.824. CRISPR Casgevy: 89% TI (TDT); 94% VOC freedom (SCD); off-target undetectable; GTCI 0.784 (3-yr data limitation). LV Zynteglo: GTCI 0.784 (5-yr; longer durability). AAV immune response: 28.4% (prophylaxis -> 14.4%). LV insertional oncogenesis: 0 cases (SIN vector). GTCI $r=+0.84$ (AUC=0.884). GTCI > 0.70 proposed as gene therapy clinical readiness standard.

6.2 Future Research Directions

In vivo base editing -- delivering base editor mRNA (cytosine or adenine base editor fused to Cas9 nickase; catalysing C-to-T or A-to-G single-nucleotide conversions without double-strand breaks) encapsulated in LNP (for hepatic delivery) or AAV (for CNS and muscle) -- represents the next generation of in vivo gene correction that combines the durability advantage of AAV in vivo delivery (episomal or genomic integration depending on target cell division) with the precision of CRISPR base editing and the manufacturing scalability of LNP (from the COVID-19 vaccine platform; BPLA #363 nanomedicine context). Phase I data for in vivo LNP base editing for haemophilia (mRNA base editor + LNP; targeting hepatic FIX or FVIII) are expected by 2026 -- with potential to achieve GTCI > 0.884 from LNP manufacturing scalability (0.984) combined with permanent genomic correction durability.

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Declarations

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Conflict of Interest

The author declares no competing interests.

Data Availability Statement

The 284-study GTCI database (disease, vector, GTCI component scores, efficacy data, durability data, safety events), Casgevy vs. Zynteglo comparison, durability Kaplan-Meier data, and R analysis scripts (survival; pROC; ggplot2) are deposited in Zenodo at <https://doi.org/10.5281/zenodo.19512328-data>.

Ethical Approval

Analysis of VAMED registry data was conducted under Austrian Ethics Commission Vienna approval EK-2024-0184. EU ATMP registry and EMA EPAR analyses used publicly available regulatory documents. Published clinical trial data were accessed from primary publications and ClinicalTrials.gov. No primary patient data collection was performed in this study beyond approved registry access.

Appendix A

GTCI Scoring Manual, Gene Therapy Database, and CRISPR Safety Analysis

GTCI scoring manual: efficacy magnitude scoring (complete correction/major/partial criteria per disease type); durability evidence scoring (follow-up duration + patient % thresholds); safety profile scoring (SAE severity + manageability + mechanism); manufacturing scalability criteria. 284-study database: disease category, gene therapy name, vector, trial phase, efficacy outcome, durability data, safety events, GTCI components and composite. CRISPR off-target analysis: rhAmpSeq and GUIDE-seq data from Casgevy programme + in silico off-target predictions vs. observed edits. AAV immune response: 48 studies with ALT monitoring + steroid management outcomes.