

Solid Biosciences: Choosing the Next DMD Gene-Therapy Bet

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Case convention: This is an author-created management decision exercise. The assignment and alternatives are hypothetical; company disclosures are historical. No private deliberations are represented.

The choice

By September 2022, Solid Biosciences had two Duchenne muscular dystrophy (DMD) gene-therapy programs at very different stages. SGT-001 had already been dosed in people and had generated encouraging but small, uncontrolled interim observations alongside a serious safety history. SGT-003 paired a next-generation capsid with Solid's microdystrophin construct, but remained preclinical. Both programs required scarce cash, specialized staff, regulatory attention, and manufacturing work.

The company's public plan still contemplated future SGT-001 dosing after a manufacturing transition and an early-to-mid-2023 SGT-003 IND submission. Yet capital and execution risk made a two-program strategy costly. How much should Solid continue to invest in the clinical learning option represented by SGT-001 while advancing SGT-003? Would concentration improve the odds that at least one program reached a meaningful clinical milestone, or would it discard valuable human evidence too early?

Assignment: Advise Solid's leadership on how to allocate resources between SGT-001 and SGT-003 as of the cutoff. Select a portfolio path, define the next decision gates, explain what should be funded, staged, paused, or partnered, and identify the evidence that would change your recommendation. Use only information available by 29 September 2022. The proposed alternatives are analytical options for this exercise, not claims about management's private plans.

A disease and a product thesis

DMD is a progressive muscle-wasting disease caused by mutations in the dystrophin gene. Solid's gene-transfer strategy sought to deliver a shortened, functional microdystrophin using an adeno-associated virus (AAV) vector. Systemic delivery could reach skeletal, cardiac, and respiratory muscle, but it also raised challenges involving vector dose, immune response, off-target exposure, durability, product quality, and manufacturing scale. AAV's packaging limits meant the delivered construct could not reproduce the full dystrophin protein.

SGT-001 used an AAV9 capsid and Solid's nNOS-containing microdystrophin construct. SGT-003 combined a different, muscle-tropic capsid called AAV-SLB101 with the same differentiated microdystrophin construct. Solid reported two distinct sets of preclinical observations: an NHP

study using AAV-SLB101 with a **reporter transgene** showed increased muscle tropism and lower liver biodistribution versus AAV9; separate mouse and cell-line studies reported microdystrophin expression. The NHP reporter result did not establish therapeutic microdystrophin efficacy in NHPs, and none of these studies established human safety, efficacy, or a lower clinical dose. [S4], [S5]

The company also planned a move toward transient-transfection manufacturing. In April 2022 it described a commercially scaled, outsourced process and said it anticipated using transfection-based manufacturing for both DMD programs. This was a forward plan; public disclosures did not establish that the preclinical SGT-003 data package used that process or that it would deliver lower cost, greater consistency, or better clinical performance. A process change could require comparability work as well as additional manufacturing and regulatory resources. [S4], [S5]

What SGT-001 had-and had not-shown

By March 2022, Solid reported that nine patients had received SGT-001, including six at 2×10^{14} vector genomes per kilogram. The company described two-year functional, pulmonary, patient-reported, and microdystrophin findings for the first three high-dose patients as favorable relative to natural-history expectations. Those observations came from a small, open-label experience, not a randomized efficacy comparison. Patient-level data, a complete prespecified analysis plan, and a fully described external-control method were not available in the public summaries reviewed. [S3]

The safety record complicated any interpretation of those signals. Holds and adverse events occurred at different times and should not be compressed into one dose-response story:

Date	Publicly reported development
November 2017-April 2018	FDA imposed a partial, higher-dose-only hold over manufacturing lot/vial capacity and process questions. FDA accepted Solid's response and resolved that partial hold on 18 April 2018, while a separate full trial hold remained active. [S11], [S15]
February-June 2018	The first participant received 5×10^{13} vg/kg, the lower dose. Days later, platelet and red-cell counts fell, with transient renal impairment and evidence of complement activation. FDA imposed a full clinical hold on 14 March and lifted it on 18 June after Solid's response and protocol changes. [S15]
Date	Publicly reported development
October 2019-October 2020	The third participant in the 2×10^{14} vg/kg cohort (sixth overall, per issuer disclosures) experienced a drug-related SAE characterized by complement activation,

Date	Publicly reported development
	thrombocytopenia, reduced red-cell count, acute kidney injury, and cardiopulmonary insufficiency. FDA imposed a separate clinical hold in November 2019. On 24 July 2020, FDA maintained the hold and requested additional manufacturing information, updated safety and efficacy data for all dosed patients, and direction on total viral load. FDA lifted the hold in October 2020 after further submissions and protocol/process changes. [S1], [S12], [S16]
April 2021	Patient 8 experienced an inflammatory-response SAE that the investigator considered drug-related. Solid said it was described in the investigator brochure, was not unexpected, and had been shared with FDA and the safety-monitoring board. The reviewed disclosures do not establish a new formal FDA hold after this event. A September 2021 company deck reported terminal complement pathway activation across all eight subjects and three complement-related SAEs overall, without assigning each event to a named patient. [S13], [S14]

The protocol, dose sequence, manufacturing work, and risk-mitigation measures changed over time and together. The public record does not isolate the effect of any one mitigation or establish a dose-response relationship. The first full hold followed the lower initial dose; the serious 2019 event followed a later high-dose infusion. Neither observation resolves the cause of the events or the residual risk of further dosing.

A contested field

Other gene-therapy programs made the timing more consequential, but their results were not directly comparable. In January 2021, Sarepta reported that its randomized Study 102 Part 1 met the microdystrophin-expression co-primary endpoint (mean 28.1% in treated patients, $n=20$, $p<.0001$), while the 48-week NSAA functional co-primary endpoint did not reach statistical significance versus placebo ($p=.37$). A prespecified younger subgroup favored treatment, while the 6-7-year subgroup had a baseline NSAA imbalance. In January 2022, Sarepta separately reported a 2-point mean NSAA difference at 48 weeks in 20 crossover-treated patients versus propensity-weighted external controls ($p=.0009$); that comparison was not against a concurrent placebo group. Its Phase 3 EMBARK trial was randomized, double-blind, and placebo-controlled, with a target enrollment of 120. [S6], [S7], [S8]

Pfizer's April 2022 release said FDA had lifted the U.S. IND hold for Cliffo and that five authorities had approved restart, while other regulatory reviews remained underway. Pfizer planned to open U.S. sites; that release did not establish a completed global restart. The earlier fatal adverse event had occurred in a non-ambulatory Phase 1b participant, and Pfizer said the protocol added seven days of hospitalization. [S9]

Mutation-specific antisense therapies-eteplirsen for mutations amenable to exon 51 skipping, golodirsen and viltolarsen for exon 53, and casimersen for exon 45-were also available to subsets. FDA had granted accelerated approval based on dystrophin increase as a surrogate. The labels said continued approval may be contingent on verification of clinical benefit; eteplirsen alone explicitly stated that clinical benefit had not been established. These drugs were not broad substitutes for an AAV gene-transfer program. [S10]

These competitor programs offered pressure and context, not a head-to-head answer. Constructs, capsids, doses, assays, populations, endpoints, and comparators differed. A positive signal in one program could not be carried over as a success probability or efficacy estimate for Solid.

Capital and operating room

Solid reported \$162.883 million in cash, cash equivalents, and available-for-sale securities at 30 June 2022, excluding \$2.070 million in restricted cash. Management expected those resources to fund operations and capital expenditure into the second quarter of 2024 under its operating plan. During the first half of 2022, Solid used \$43.068 million of cash in operating activities and recorded \$43.125 million in R&D expense. [S1], [S2]

The company disclosed some historical R&D allocation, but not a forward budget for either candidate:

Exhibit 1. Selected financial facts at the cutoff

USD millions, except per-month calculation. Company facts are distinguished from calculations.

Measure	Amount	Classification and source
Cash and cash equivalents, 30 June 2022	\$54.311	Reported fact. SEC Form 10-Q, balance sheet, p. 2. [S1]
Available-for-sale securities, 30 June 2022	\$108.572	Reported fact. SEC Form 10-Q, balance sheet, p. 2. [S1]

Measure	Amount	Classification and source
Cash plus securities, excluding restricted cash	\$162.883	Derived: \$54.311m + \$108.572m. [S1]
H1 2022 net cash used in operating activities	\$43.068	Reported fact, cash-flow statement, p. 7; not R&D-only or a forward burn rate. [S1]
H1 2022 R&D expense	\$43.125	Reported fact, accrual expense, statements of operations, p. 3. [S1]
Simple average H1 operating cash use	\$7.178/month	Derived: \$43.068m ÷ 6 months. Historical reference only, not a forecast.
Simple cash/securities-to-average-use ratio	22.7 months	Derived: \$162.883m ÷ \$7.178m. Not management's runway forecast and not a candidate-level funding estimate.
Management runway estimate	Into Q2 2024	Management estimate using its operating plan; not a fixed expiry or independent forecast. [S1], [S2]

Exhibit 2. Reported H1 2022 R&D allocation

USD millions, converted from the filing's USD thousands; all rows are accrual expense, not cash spend.

Category	Amount	What the category does-and does not-show
SGT-001	\$18.220	Reported allocated expense; excludes some shared costs. [S1]
SGT-003 and other development programs	\$4.587	Combined amount, not a stand-alone SGT-003 figure. [S1]
Unallocated	\$20.318	Personnel \$14.283m plus external \$6.035m; not program-specific. [S1]
Total R&D	\$43.125	Reconciles to the H1 income statement. [S1]

The figures allow a rough cash-resource discussion, but they do not answer how much incremental funding each plan would require. The R&D categories are backward-looking accounting expenses; the company did not disclose remaining SGT-001 process-transition costs, the cost to reach an SGT-003 IND, the minimum cost of preserving a paused program, candidate-specific staffing, or partner economics. Cash use, R&D expense, and net loss are different measures.

Possible paths

1. **Continue both programs.** Preserve the human-learning option in SGT-001 while advancing SGT-003 through IND-enabling work. This may retain more scientific options and could use the SGT-001 clinical experience to inform the shared construct. It also maintains competing claims on cash, talent, and manufacturing/regulatory attention, and leaves unresolved safety and comparability questions.
2. **Concentrate on SGT-003.** Put the DMD portfolio behind the new capsid/construct combination and its planned IND path. This simplifies the allocation choice and concentrates organizational effort, but trades away near-term SGT-001 learning and places more weight on sponsor-reported preclinical translation.
3. **Stage the portfolio.** Fund SGT-003 to defined technical and regulatory gates while preserving SGT-001 monitoring and a limited, explicitly costed option to reconsider further development. Set conditions for re-entry, pause, or exit. This could limit commitment before learning arrives, but a “cheap” preservation strategy may not be feasible if shared resources, process comparability, or regulatory obligations carry fixed costs.

Partnership or licensing could alter the resource trade-off, but no public disclosure at the cutoff established an available offer or acceptable economics. Treat it as a route to investigate, not as committed financing.

Your recommendation

Write a two-page portfolio memo that:

- selects a path and explains why the evidence supports it;
- names the next decision gates for each program and the facts you would require before releasing additional capital;
- uses the cash and R&D exhibits to construct a conditional resource/runway view, while labeling assumptions and explaining why historical averages are not a forecast;
- addresses patient-safety monitoring, manufacturing comparability, regulatory engagement, and how Solid should preserve or redirect scarce expertise; and
- identifies the strongest argument against your choice and the evidence that would make you reverse it.

Do not use clinical success probabilities or program costs that the public record does not support. If you use assumed costs, label them as assumptions and show how your recommendation changes when they move.

Sources and conventions

All source versions and detailed reading locators are in the company research dossier’s source register. Direct primary sources are identified below. Company statements about efficacy, preclinical comparisons, and expected milestones are attributed; competitor reports are not head-to-head evidence.

- **S1.** Solid Biosciences, [Q2 2022 Form 10-Q](#), filed 11 Aug 2022; balance sheet p. 2, operations p. 3, cash flows p. 7, R&D allocation p. 21.
- **S2.** Solid Biosciences, [Q2 2022 business update](#), 11 Aug 2022; pipeline and financial highlights.

- **S3.** Solid Biosciences, [FY2021 results and two-year SGT-001 update](#), 14 Mar 2022; “SGT-001 Update” and “Efficacy and Safety Data.”
- **S4.** Solid Biosciences, [updated corporate strategy](#), 27 Apr 2022; manufacturing and SGT-003 update.
- **S5.** Solid Biosciences, [Q2 2022 business update](#), 11 Aug 2022; SGT-003 update.
- **S6.** Sarepta, [Study 102 Part 1 topline results](#), 7 Jan 2021.
- **S7.** Sarepta, [Study 102 Part 2 results](#), 10 Jan 2022.
- **S8.** Sarepta, [EMBARK and gene-therapy update](#), 6 Jul 2022; full issuer-distributed syndication read; issuer page returned HTTP 403.
- **S9.** Pfizer, [CIFFREO update](#), 28 Apr 2022.
- **S10.** FDA, [eteplirsén](#), [golodirsén](#), [viltolarsén](#), and [casimersén](#) labels; see research source register P25-P26 for indications and approval caveats.
- **S11.** Solid Biosciences, [18 Apr 2018 SGT-001 update](#); separate partial-hold resolution and full-hold status.
- **S12.** Solid Biosciences, [24 Jul 2020 clinical-hold update](#); full release read; see SEC Form 8-K and 10-Q in research source register P29.
- **S13.** Solid Biosciences, [14 May 2021 community update](#); patient-8 SAE disclosure.
- **S14.** Solid Biosciences, [September 2021 safety update](#), slide 9 / printed p. 7.
- **S15.** Solid Biosciences, [18 Jun 2018 full clinical-hold lift](#); protocol changes and resumption activities.
- **S16.** Solid Biosciences, [1 Oct 2020 full clinical-hold lift](#); protocol, safety and manufacturing/comparability update.