Evaluate Vantage

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Gene therapy data shake Solid

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Better-looking safety might not be enough to get Solid back in the Duchenne muscular dystrophy game.

First, the good news for Solid Biosciences: the new process put in place for its Duchenne muscular dystrophy gene therapy project SGT-001 looks safe. Next, the bad: interim data from the phase I/II Ignite DMD trial are disappointing, and the group's stock slid 24% this morning.

Notably, SGT-001's performance at one year on a key clinical measure, the North Star Ambulatory Assessment (NSAA), was worse than that of Sarepta's SRP-9001 in that project's failed phase II Study 102.

Caution should be taken when interpreting cross-trial comparisons, but the data are a blow to Solid's claims of differentiation with SGT-001. Both SGT-001 and SRP-9001 are designed to increase the production of microdystrophin, a shortened version of the dystrophin protein that is missing in DMD patients.

Solid hopes that by also including a neuronal nitric oxide synthase (nNOS) binding domain its project could lead to greater improvements in muscle function than with other gene therapies.

Ignite fizzles

So far, this theory does not seem to have been borne out, although the Ignite DMD data are tricky to interpret, coming from just six subjects in a single-arm study. As a control, Solid also reported data from three patients in the same trial who had not yet been treated.

On the NSAA, the lack of dose response could be a red flag. And even the one-point improvement seen in the low-dose group looks unfavourable versus the 1.7-point gain in the NSAA seen in Sarepta's Study 102, which saw a high placebo response (*Gene therapy trial fails to rectify Sarepta's sorry record, January 8, 2021*).

Leerink analysts cautioned against making this cross-trial comparison, especially given that Sarepta's trial assessed younger patients with lower baseline NSAA scores versus Ignite DMD.

Indeed, high baseline NSAA scores were flagged by Solid, whose acting chief medical officer, Cathryn Clary, said during a conference call yesterday that this might have made it difficult to show an improvement at one year in Ignite DMD.

She argued that the "totality of the data" should be taken into account, and it is true that SGT-001 showed more consistency on other endpoints, such as the six-minute walk test and forced vital capacity.

However, there were confusing results with one biomarker, creatinine, a product of muscle breakdown. Decreases could indicate improved integrity of muscle fibres, but increases were seen in two patients in the low-dose SGT-001 group.

Not so Solid? Interim data from Ignite DMD			
Endpoint	**Low-dose (5e13vg/kg, n=3)**	**High-dose (2e14vg/kg, n=3)**	**Delayed treatment control (n=3)**
NSAA score	+1.0 point	+0.3 points	-4.0 points
6MWT distance	+37.0m	+49.7m	-8.5m
FVC	+3.9%	+16.7%	-10.7%
CK	+166%	-50%	+17%
All mean values at 1 year; NSAA = North Star Ambulatory Assessment; 6MWT = six-minute walk test; FVC = forced vital capacity; CK = creatinine kinase. Source: company presentation.			

SVB Leerink analysts were “encouraged” by the data; more cautious Evercore ISI analysts wrote that there were “some potential signs of response”, adding that the small participant numbers and inter-patient variability on outcomes made it hard to discern a clear signal.

At least Solid can breathe easier on safety, based on the experience of one patient. Ignite DMD was put on clinical hold twice owing to serious adverse events, most recently in November 2019. In both cases signs of complement activation were seen.

The FDA lifted the latest hold last October. A seventh subject has now been treated using a second-generation manufacturing process to decrease total viral load, and a clinical mitigation strategy that included pre-treatment with Alexion’s Soliris, a complement inhibitor.

Solid said yesterday that this patient had experienced “transient and manageable” adverse events, none of which were serious, and no pathological complement activation.

But adding a costly drug on top of an already expensive gene therapy might hurt SGT-001’s chances if it does make it to market, particularly as Sarepta’s SRP-9001 does not require Soliris prophylaxis. Despite the Study 102 failure, Sarepta is pressing on and could start a pivotal trial of its project, which is licensed to Roche outside the US, by mid-year.

Meanwhile, the companies’ other main DMD gene therapy competitor, Pfizer, has also seen signs of complement activation in its phase I study of PF-06939926; that project is in a phase III trial called Ciffreo.