Evaluate Vantage

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Zynerba fragile after pivotal failure

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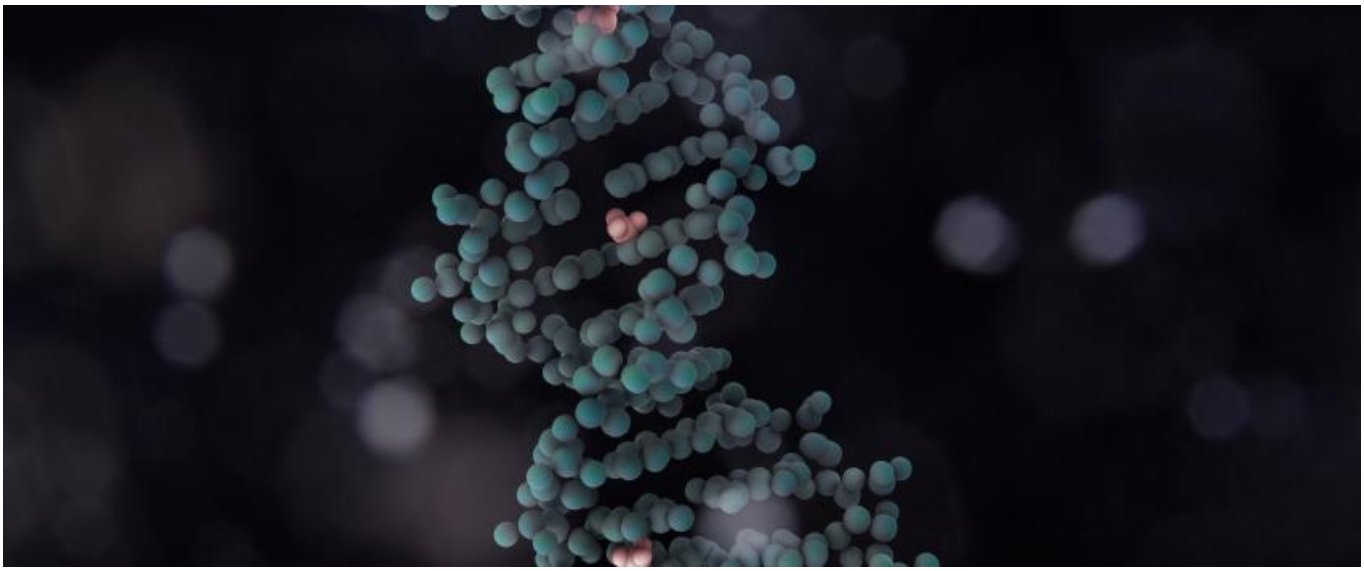

The implosion of Zygel's fragile X study leaves its developer few places to turn.

Before the pivotal trial of Zynerba's Zygel reported topline data today, every attempt to treat fragile X syndrome had failed. Sadly for Zynerba, down 48% in early trade, the same remains true now.

The company had hoped that a near miss on the primary endpoint of the Connect-FX trial might still be good enough for filing, if the secondary measures were hit. The cannabinoid gel actually missed the primary by a mile, and hit precisely none of the secondaries. The company claims that it might have found a way forward with a subgroup analysis, but even here the hit is hardly emphatic.

Connect-FX was designed to show an improvement over placebo on the social avoidance subscale of the aberrant behaviour checklist (ABC) as its primary outcome measure, with the company telling *Evaluate Vantage* four months ago that it was looking for an improvement of 20 percentage points over placebo (*Zynerba hopes to crack fragile X at last, March 5, 2020*).

The data actually show a placebo-adjusted benefit of just six points, and neither this endpoint nor any of the others hit statistical significance.

Connect-FX results in total study population					
	Zygel (n=109)		Placebo (n=101)		
Endpoint	**Change at wk 12**	**Percentage change**	**Change at wk 12**	**Percentage change**	**Difference (percentage points)**
ABC-C_{FXS} social avoidance subscale	-2.7	-38%	-2.3	-32%	-6
ABC-C_{FXS} irritability subscale	-5.9	-21%	-4.1	-15%	-6
ABC-C_{FXS} socially unresponsive / lethargy subscale	-3.5	-26%	-3.1	-24%	-2
CGI-I at week 12 (much and very much improved)	20%		16%		4
ABC-C_{FXS}=aberrant behaviour checklist-community FXS. CGI-I=improvement in clinical global impression. Source: company press release.					

Safety was clean enough, with 14 treatment-related adverse events in the Zygel cohort versus six in the placebo group. The most common treatment-related event was application site pain, seen in 6% and 1% of Zygel and placebo subjects respectively.

Full methyl jacket

The company is pinning its hopes for a path forward to a planned analysis of patients in the study who had at least 90% methylation – known as full methylation – of the gene associated with fragile X, *FMR1*.

Methylation is an epigenetic process whereby a methyl group is placed on the backbone of the DNA. Full methylation of *FMR1* results in decreased or silenced transcription of the gene, and fragile X patients with full methylation of *FMR1* are more severely ill, Zynerba says.

In this population, which made up around 80% of the participants in Connect-FX, Zygel achieved a p value below 0.05 on the social avoidance subscale; despite all main metrics being missed, Zynerba claimed that this was "statistically significant" versus placebo. None of the secondaries showed a nominal hit in the fully methylated subgroup.

Connect-FX results in fully methylated patients						
	Zygel (n=91)		Placebo (n=76)			
Endpoint	**Change at wk 12**	**Percentage change**	**Change at wk 12**	**Percentage change**	**Difference (percentage points)**	**P value**
ABC-C_{FXS} social avoidance subscale	-3.0	-42%	-2.0	-10%	-18	0.020
ABC-C_{FXS} irritability subscale	-6.4	-22%	-4.1	-1%	-14	0.091
ABC-C_{FXS} socially unresponsive / lethargy subscale	-3.9	-29%	-2.7	-3%	-18	0.135
CGI-I at week 12 (much and very much improved)	51%		36%		15	0.056
ABC-C_{FXS}=aberrant behaviour checklist-community FXS. CGI-I=improvement in clinical global impression. Source: company press release.						

Challenged on a conference call to provide a mechanistic rationale for Zygel's better performance in fully methylated patients, management said only than that when the *FMR1* gene did not function "things fall apart,

and one of those things is the endocannabinoid pathway”.

On the plus side testing for methylation is fairly straightforward and costs around $350, the company said.

Confirmation?

Nothing daunted, the group intends to ask the US FDA as soon as possible whether it can submit the Connect-FX dataset for approval in fully methylated patients. The alternative will be conducting a trial in this specific population, and given that Connect-FX took two years such a requirement would push the timelines out markedly.

Zynerba had around $60m in cash at the end of June, enough to last to the second half of next year. It had planned to recruit more staff, presumably sales people, immediately after the Connect-FX readout; this will now not happen, potentially extending the cash runway, but more cash will be needed if another trial is necessary

Moreover, while 80% of the trial population were fully methylated, only around 60% of the general fragile X population carries this biomarker. If Zygel is approved in this subset, with or without a confirmatory trial, its potential market is cut down from around 71,000 US patients to around 40,000.

Zygel is Zynerba’s sole asset, and though it is developing the gel for other indications fragile X was by far the most advanced. One way and another the way ahead looks very rocky.