

VTV pivots to diabetes after Alzheimer's flop



[Madeleine Armstrong](#)

Pulling off a pivotal trial win in Alzheimer's was always going to be hard for VTV Therapeutics' Rage inhibitor azeliragon. But the collapse of the company's value today suggests inexplicable optimism among investors in the run-up to the results.

Azeliragon's failure is yet another reminder of how tough Alzheimer's drug development is, ahead of the most hyped upcoming readout in the space, that of the phase III trial of Biogen's anti-amyloid MAb aducanumab in early 2020. At least VTV has a plan B in the form of its diabetes pipeline, though the market's reaction suggests that no one is expecting much here (see tables below).

Competition could stymie the group's ambitions in diabetes - while VTV is convinced that its small-molecule GLP-1 agonist TTP273 is cleaner than existing drugs in this class, the group has been forced to focus on China initially because of a lack of interest from US partners.

And now to diabetes - VTV's pipeline

Project	Indication	Mechanism	Status	Trial(s)
Azeliragon	Alzheimer's disease	Rage antagonist	Failed phase III	Steadfast, part A & B (NCT02080364)
TTP273*	Type 2 diabetes	Oral GLP-1 receptor agonist	Phase II	-
TTP399	Type 1 diabetes	Glucokinase stimulant	Phase II	SimpliciT1 (NCT03335371)**
HPP971	Inflammation	Bach1 inhibitor	Phase I	-
HPP737	Inflammation	PDE4 inhibitor	Phase I	-
HPP593	Musculoskeletal disorders	PPAR-delta agonist	Phase I	-

**Partnered with Huadong Medicine; **trial in partnership with the Juvenile Diabetes Research Foundation. Source: company website, EvaluatePharma.*

At least VTV looks unlikely to throw good money after bad in Alzheimer's after azeliragon fell short in part A of the Steadfast trial. The company has discontinued all further studies of the project, including Steadfast part B, which was due to report data by the end of the year.

VTV executives previously told *EP Vantage* that the company could not afford to start a new trial of azeliragon, for example in earlier-stage Alzheimer's, an approach taken by some other companies with failed Alzheimer's drugs ([Interview - VTV aims to make novel Alzheimer's target all the Rage, February 5, 2018](#)).

The only way forward for azeliragon would therefore appear to be via a larger partner - and it is difficult to see who might be interested. Steadfast part A results with azeliragon were similar to those seen with placebo on cognitive or functional outcomes, as measured by the Adas-Cog subscale and the clinical dementia rating scale sum of boxes.

As well as being the latest in a long line of Alzheimer's flops, azeliragon's failure is also another nail in the coffin for the amyloid hypothesis. Rage, which stands for receptor for advanced glycation end-products, is thought to lie upstream of three key targets in Alzheimer's: amyloid-beta, Tau and inflammation.

This might not bode well for aducanumab, which targets amyloid. Doubts about the Biogen project had already been growing since February, when the company increased the size of its pivotal trials and delayed readout until early 2020 ([Snippet roundup: Alzheimer's doubts grow and Bavencio's Javelin falls short, February 16, 2018](#)).

And expectations for Bace inhibitors have been low since failures with Merck & Co's verubecestat, most recently in prodromal disease.

Selected upcoming late-stage Alzheimer's readouts					
Project	Company	Mechanism	Trial	Population	Primary completion
Lanabecestat	Astrazeneca/Lilly	Bace inhibitor	Daybreak-Alz, NCT02783573	Mild AD	Sep 2019
			Amaranth, NCT02245737	Early AD	Sep 2019
Aducanumab	Biogen	Anti-beta-amyloid MAb	Engage, NCT02477800	Early AD	Nov 2019
			Emerge, NCT02484547	Early AD	Feb 2020
Crenezumab	Roche	Anti-beta-amyloid MAb	Cread, NCT02670083	Prodromal to mild AD	Aug 2020
			Cread2, NCT03114657	Prodromal to mild AD	Oct 2021
Elenbecestat	Eisai/Biogen	Bace inhibitor	MissionAD1, NCT02956486	Early AD	Nov 2020
			MissionAD2, NCT03036280	Early AD	Nov 2020
Solanezumab	Lilly	Anti-beta-amyloid MAb	A4, NCT02008357	Preclinical AD	Jul 2022

Source: EvaluatePharma, Clinicaltrials.gov.

Still, various setbacks have failed to dent the amyloid hypothesis so far – remarkably, in spite of its earlier failures Lilly's solanezumab is still going in phase III, in a study in older people with no symptoms of cognitive impairment or dementia.

An [NEJM editorial](#) earlier this year noted that it would be foolish to ignore the continued failures of anti-amyloid approaches. It is unclear what it might take to make the biopharma industry let go of its amyloid fixation.

Diabetes

This is no longer a worry for VTV, which will now have to concern itself with a crowded diabetes market.

The company's chief executive, Stephen Holcombe, previously told *EP Vantage* that attracting a US partner for the GLP-1 agonist TTP273 had been difficult. According to Mr Holcombe, VTV's candidate is as good as what is already on the market in terms of HbA1c and weight loss, but prospective partners wanted superiority given pricing pressure in the US.

"Instead we went to China. If we do have better efficacy we will come back to the US," he added. He believes that, being an oral small molecule, TTP273 could avoid the nausea and vomiting seen with Novo Nordisk's oral formulation of semaglutide. The other GLP-1s are injectable.

Under an agreement with Huadong Medicine in December, VTV will conduct a multi-regional phase II trial of TTP273 and will then receive \$8m – not to be sniffed at by a company that had just \$11.8m in cash at the end of the year.

Meanwhile, VTV is steering clear of type 2 diabetes and going for the less busy type 1 space with its glucokinase stimulant TTP399. It just completed enrolment in the phase I portion of the SimpliciT1 study being carried out with the Juvenile Diabetes Research Foundation.

Although VTV has been wise not to put all its eggs in the Alzheimer's basket, in diabetes it has chosen another market that will be difficult to break, albeit for different reasons. With funds running low, it is unclear how long the group will be able to keep trying.

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