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Rett failure sets up thin pipeline

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Newron’s failure in Rett syndrome leaves the late-stage pipeline to GW Pharma, Acadia and Anavex.

Newron’s pivotal Stars study, testing sarizotan in Rett syndrome, was always a high risk bet − the company lacked any human data on the project before starting the trial. Stars duly missed its primary endpoint, and Newron’s shares have tanked 70% today.

The company has now scrapped the whole Rett programme, a blow for a therapy area with no approved products. Candidates from GW Pharma, Acadia and Anavex are next in line but, like sarizotan, focus on treating symptoms rather than the disorder’s underlying cause.

Rett syndrome almost exclusively affects girls and is caused by a mutation on the X chromosome in the *MECP2* gene, which encodes a protein involved in the development of the central nervous system, especially synaptic and circuit maturation. Following apparently normal development for the first six months of life patients experience a decline in hand use and communication and many have recurrent seizures, as well as a variety of motor problems including increased muscle tone and abnormal movements.

Behind sarizotan in the development pipeline is Anavex’s therapy Anavex 2-73, a small-molecule activator of the sigma-1 receptor. Data from six adult patients from the open-label portion of the phase II study showed improvements in scores on both the Rett syndrome behaviour questionnaire (RSBQ) and the clinical global impression-improvement (CGI-I) scale at seven weeks.

Data from the placebo-controlled part of the trial in 15 patients ought to provide more compelling evidence, and are expected in the second half of the year. A second phase II study called Avatar, being conducted in Australia, could also report this year, while the phase II/III paediatric Excellence study is not due to report until 2021.

Phase III pipeline for Rett syndrome					
Product	**Company**	**Mechanism of action**	**Indication sales 2026e ($m)**	**Clinical trial note**	**Primar endpoi**
Sarizotan	Newron Pharmaceuticals	5-HT1A receptor agonist; dopamine D2 receptor antagonist	126*	Pivotal Stars failed	Reducti in respirat abnorm
Trofinetide Oral	Acadia Pharmaceuticals	Insulin-like growth factor 1 regulator	116	Lavender, Sep 2021	RSBQ,C at 12 w
Anavex 2-73 (blarcamesine)	Anavex Life Sciences/Neuren Pharmaceuticals	Muscarinic acetylcholine receptor regulator; Sigma-1 receptor agonist	114	Data expected H2 from NCT03758924 and Avatar. Ph II/III Excellence, June 2021	RSBQ,C at 12 w (Excelle study)
Epidiolex	GW Pharmaceuticals	Cannabinoid receptor agonist	35	Arch Aug 2021	RSBQ,C at 24 w
**Forecast before clinical failure. RSBQ: Rett syndrome behaviour questionnaire total score, C clinical global impression-improvement. Source: company releases, EvaluatePharma.*					

In the clinic

GW's attention to Rett syndrome is understandable. The company's cannabinoid Epidiolex is already on the market for the rare childhood epilepsy conditions Dravet and Lennox-Gastaut and is filed in tuberous sclerosis complex. The drug was able reduce the frequency of seizures in the epilepsy conditions and 2026 sales are forecast to reach $1.6bn according to consensus from *EvaluatePharma*, with a tiny portion, $35m, expected from Rett syndrome.

The phase III Rett study, Arch, is recruiting 252 patients aged two to 18. Two doses of Epidiolex are being tested versus placebo for 24 weeks, again improvements in RSBQ and CGI-I scores are the primary endpoint. The study has a primary completion date of August next year.

Acadia's trofinetide is an analogue of the neuropeptide IGF-1 that the company says can reduce neuroinflammation and support synaptic function. The phase III Lavender study is a 12-week placebo-controlled trial that uses the RSBQ and CGI-I scores as the primary endpoints.

The trial, which started last November, aimed to recruit 180 patients aged five to 20, but in March the company announced that no new patients would be enrolled due to the Covid-19 pandemic. Previously enrolled patients will continue in the study, although it is not clear how large this cohort is. Results are expected next year.

A disease-modifying approach using gene therapy is the ultimate treatment goal for Retts, but these are still some way off. Sarepta Therapeutics teamed up with StrideBio at the end of last year, with Stride leading the early R&D on four CNS targets, including one for Rett syndrome. And an IND for Novartis's gene therapy AVXS-201, gained through its Avexis acquisition, is not expected until 2023.

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