Evaluate Vantage

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Puretech’s cautionary tale about pivotal study read-across

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The healthcare company builder Puretech registers one success and one failure, both underlining the need for robust mid-stage data.

It’s vital to have robust phase II results in hand before rolling the dice and ploughing into pivotal development. Puretech Health’s affiliate Karuna probably has enough after today’s mid-stage win in schizophrenia and psychosis, but caution is warranted as CNS projects often struggle to replicate in phase III the positive results seen earlier.

And, whether you’re in CNS or not, no amount of dressing up bad data can avert a later disaster, as Puretech itself has found out. On Friday the lead asset of another of its affiliates, Restorbio, bombed in phase III – an outcome that was highly predictable given that phase II data reported last year were at best mixed.

For Restorbio the writing had been on the wall ever since the company trumpeted a success with RTB101 in a phase II trial aiming to reduce the incidence of respiratory tract infections in elderly patients. In fact both the data and the way these were analysed were flawed, as *Vantage* argued at the time (*Restorbio clutches at straws, and investors say that’s fine, July 25, 2019*).

Little wonder that, after Restorbio pushed on into phase III regardless of the red flags, the later study blew up in its face. On Friday the group crashed 86% after saying that the pivotal Protector-1 trial was a bust, and that RTB101 development in elderly people’s respiratory disease would be halted.

Numerically, subjects actually did worse on RTB101 than on placebo, according to Protector-1’s primary endpoint. The group said it wanted to understand “the difference in RTB101 activity observed in Protector-1 as compared to prior phase II studies”, apparently forgetting that phase II was nothing to write home about.

Karuna's win

At least there is better news for Karuna, whose KarXT today overcame its first hurdle, with impressive results in a phase II trial in schizophrenia and acute psychosis, causing shares to rocket 214% in early trading. The company now has a market cap of $1.3bn.

The 182-patient study showed a placebo-adjusted 11.6-point mean reduction in total Positive and Negative Syndrome Scale (PANSS) score at week 5, a statistically significant result. Karuna noted that antipsychotics had historically been approved on a five-point minimum improvement.

Between treatment and placebo there were also similar rates of weight gain and somnolence, issues that have often plagued older schizophrenia drugs.

The Karuna project contains trospium chloride and xanomeline; the latter active ingredient was originated at Lilly, which showed a placebo-adjusted 24-point total PANSS score change in a small schizophrenia trial. However, there was an association with cholinergic adverse events, such as excessive sweating, nausea, vomiting and diarrhoea, necessitating its co-formulation with trospium chloride, a muscarinic receptor antagonist, to mitigate the side effects.

For Karuna phase III is where the real test lies: it is often the case that with larger CNS trials the effect sizes narrow. The improvement seen by placebo patients in Karuna's phase II study, an average decrease of 5.9 points, is on the lower side of what is typically seen in the control arms of schizophrenia studies, but the company put this down to the design of the trial.

Karuna expect to start phase III by the end of next year, while early trials in pain and Alzheimer's disease psychosis are due to read out in the second half of 2020. For Puretech, which owns around 30% of Karuna and Restorbio, this is quite the turnaround; the company fell 10% on Friday, but today's 12% rise erased its losses.