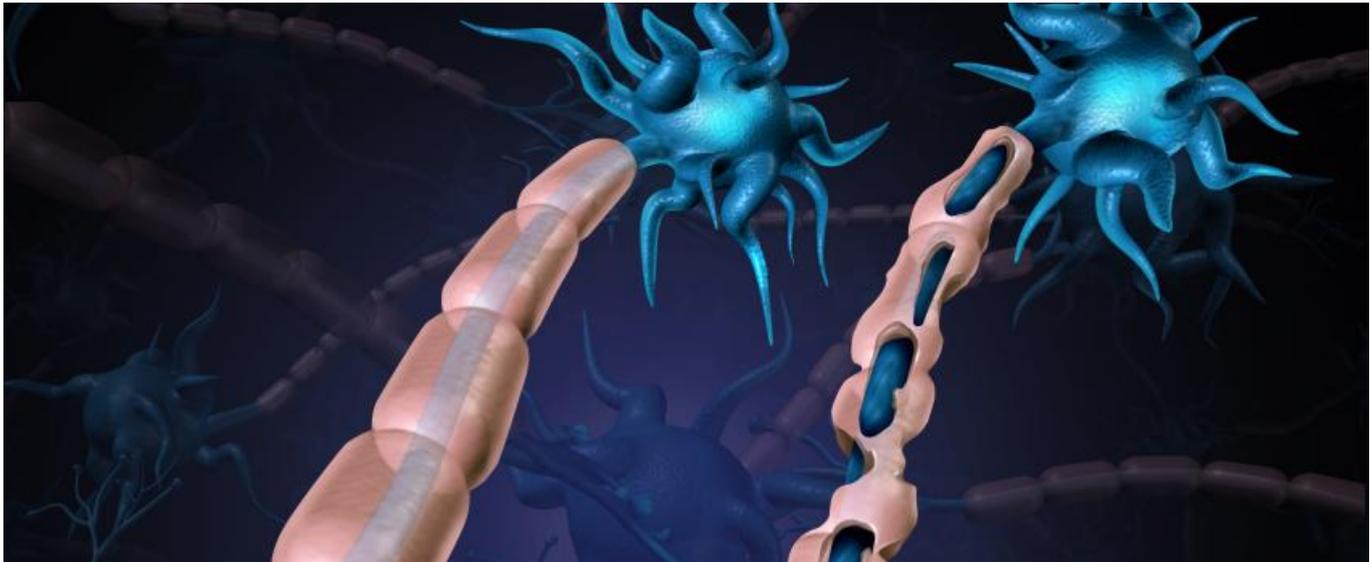


Multiple sclerosis “win” makes the Principia shorts squirm



[Jacob Plieth](#)



Investors betting on the Principia short thesis face up to a clinical trial success that might not be what it seems.

A positive clinical trial in multiple sclerosis with a mechanism that has so far failed to deliver would normally be hailed as a major medical advance. In the case of Principia’s BTK inhibitor SAR442168, however, the win is by no means clear-cut.

SAR442168’s mid-stage study had such a convoluted design that a detailed analysis is needed to tease out its real benefit, and right now Sanofi – Principia’s partner, which [this morning announced](#) that the trial’s primary endpoint had been met – is not providing this detail. Nevertheless, investors who had gone short Principia will today be feeling increasingly uncomfortable.

The Principia short thesis centres on the shortcomings of BTK inhibition, and had been [laid out by the investment firm Kerrisdale Capital on January 27](#). Even before this the short interest in the stock had been creeping up, amounting to almost 6% of the outstanding capital in the middle of last month.

Today the shares were up 7% in the premarket before opening up 2%, meaning that short sellers were facing the uninviting prospect of deciding whether to take the loss now, or hold out for a disappointment down the line in the knowledge that a further lift would ramp up their losses even more.

Multi-cohort crossover

The [study topline today](#) enrolled only 128 subjects with relapsing multiple sclerosis, yet had no fewer than eight cohorts, comprising four different doses given either before or after placebo.

Moreover, its primary endpoint did not relate to relapse rates or MS progression, but the number of new Gd-enhancing T1 hyperintense lesions. Investors should ask themselves on what basis a trial with such a complex design, measuring an MRI surrogate endpoint, can be said to have yielded a positive result.

Sanofi, which had [paid Principia \\$40m](#) up front two years ago for SAR442168 (then coded PRN2246), today claimed that the compound could become the first disease-modifying therapy to address sources of MS damage in the brain. It said the trial showed a dose-response relationship that would be used to determine the phase III dose.

SAR442168 pivotal multiple sclerosis studies starting mid-2020

Type of MS	Relapsing-remitting	Primary progressive	Secondary progressive
Control	Aubagio	Placebo	Placebo
Filing target	H1 2024	H1 2025	H1 2025

Source: Sanofi presentation.

Like CD20-targeting approaches, of which Roche's Ocrevus is the most impressive example, BTK inhibition relies on the theory that B cells are involved in MS. Unfortunately, virtually no evidence exists to back the use of a BTK inhibitor in MS, and SAR442168 is one of only three such agents in development for the disease.

Merck KGaA's evobrutinib was initially said to have succeeded in phase II, but it subsequently fell foul of statistical analysis rules, and was associated with liver enzyme elevations ([German Merck watches evobrutinib's benefit melt away, June 20, 2019](#)).

Even if evobrutinib and SAR442168 had managed to yield clean phase II wins the results might not have amounted to much given that they were both up against placebo. The real-world comparator is Ocrevus, and a head to head trial would clearly present a much higher bar to clear.

Nevertheless, Sanofi highlighted SAR442168's brain penetration, and said four pivotal studies would now be initiated.

This, of course, is where the problem lies for Principia short sellers. They might very well be right in thinking that SAR442168 is a dud, and in time their view could be proved right. However, with a rising share price in the meantime, and the risk of losing more and more money, continuing to short Principia will take nerves of steel.

[More from Evaluate Vantage](#)

Evaluate HQ
[44-\(0\)20-7377-0800](#)

Evaluate Americas
[+1-617-573-9450](#)

Evaluate APAC
[+81-\(0\)80-1164-4754](#)

© Copyright 2022 Evaluate Ltd.