Evaluate Vantage

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Atea and Roche get a Covid-19 antiviral warning

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The failure of the phase 2 Moonsong outpatient trial prompts a phase 3 rethink and a one-year delay.

Down but not yet out. This is probably the best way to describe Atea and Roche's Covid-19 oral antiviral candidate AT-527 after the failure of the phase 2 Moonsong trial in non-hospitalised patients.

The project will now be delayed for around a year; good news for Merck & Co, whose rival antiviral molnupiravir recently prevailed in phase 3 and was filed for emergency use authorisation last week. The latest news raises questions about trial design, in particular because Moonsong allowed vaccinated subjects, while Merck's Move-Out trial of molnupiravir did not.

Unlike Atea and Roche, Merck also focused on patients with underlying health conditions, who are at greater risk of developing severe Covid-19.

Morninsky red flags

This looks like a canny move by Merck, and a misstep by Atea and Roche, which are now scrabbling to save AT-527's ongoing pivotal study, Morningsky. That trial, like Moonsong, includes vaccinated participants and does not select for those with underlying illness.

However, it looks like this will soon change, with the groups planning major amendments that will push Morningsky's readout back to the second half of 2022; the study had been expected to yield data by the end of this year.

During a conference call today Atea's chief development officer, Janet Hammond, said: "One thing we'd want to do would be eliminate patients who've been vaccinated."

A focus on those with underlying conditions also looks likely. "It's really the high-risk patients where one is going to have the greatest likelihood of seeing an impact clinically," she added, suggesting that Moonsong might simply have been insufficiently powered to detect a small benefit.

In addition, Atea is considering changing the primary endpoint of Morningsky, which currently is time to improvement in Covid-19 symptoms. Harder endpoints like hospitalisation and death, as per molnupiravir's Move-Out trial, might be preferable.

Atea execs would not say how many patients have been enrolled in Morningsky so far and whether any of these patients' data could be used in the revised trial.

Moonsong out of tune

Atea execs found explanations for Moonsong's failure, including the rise of variants and the evolving vaccine landscape, but it has long been known that young, fit people are unlikely to develop severe Covid-19. This means that it was always going to be difficult to show a large benefit over placebo here.

The average age in the study was 37, and the median BMI less than 27. Two thirds of subjects did not have an underlying illness.

Neither dose of AT-527, 550mg or 1,100mg twice daily, met the primary endpoint, reduction in viral load versus placebo.

However, a subgroup analysis of patients with underlying health conditions did find a $0.5\log_{10}$ reduction in viral load versus placebo at day seven with both doses. Evercore ISI's Umer Raffat noted that this was comparable to the result seen with molnupiravir.

Even if Atea and Roche can salvage something from Morningsky, AT-527 could well end up an also-ran. Investors sent Atea's shares down 65% this morning.

And what might these results mean for the rest of the Covid-19 antiviral pipeline? Perhaps that those that excluded vaccinated patients – like Pfizer, which is up next with a readout – might have a better chance of success.

Selected oral antivirals for treating Covid-19

Project	Company	Setting	Trial	Vaccinated people allowed?
Molnupiravir	Merck & Co/Ridgeback	Outpatient treatment	Move-Out, succeeded	No
		Post-exposure prophylaxis	Move-Ahead, data H1 2022	No
AT-527	Roche/Atea	Outpatient treatment	Ph2 Moonsong, failed	Yes
			Morningsky, data now due H2 2022	Yes if vaccinated >40 days previously
PF-07321332	Pfizer	Low-risk outpatient treatment	NCT05011513, ends Oct 2021	No, except those with underlying condition
		High-risk outpatient treatment	NCT04960202, ends Dec 2021 (prev Nov 2021)	No
		Post-exposure prophylaxis	NCT05047601, data H1 2022	No
Favipiravir	Appili	Outpatient treatment	Preseco, ended Sep 2021	Yes
Tempol (MBM-02)	Adamis Pharmaceuticals	Outpatient treatment	NCT04729595, ends Jun 2022	No
RHB-107 (upamostat)	Redhill Biopharma	Outpatient treatment	NCT04723537, ends Sep 2022	Yes

Source: Evaluate Pharma & clinicaltrials.gov.

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