Evaluate Vantage

April 24, 2020

One leak good, two leaks bad for Gilead

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Skittish investors overreact to incomplete Covid-19 data once more – this time in the opposite direction.

Late yesterday the non-biotech investment world found out what industry specialists already know: a drug's chances of success hinge largely on trial design. Data from a Chinese trial of Gilead Sciences' remdesivir in severe Covid-19, posted by accident by the WHO, suggested that the study was a bust, and had major repercussions for the jittery markets.

Trading of Gilead shares was briefly halted when the data emerged, but the company closed down just 4% yesterday. More important are the wider effects as investors considered the possibility that remdesivir might not in fact be a quick and easy cure that will allow the swift resumption of normal working life. The S&P 500 closed down 0.1% yesterday, reversing its gain of 1.6% in the morning.

The WHO's report summarises results from 237 patients with severe disease in a now-terminated study, stating that Gilead's antiviral was not associated with a difference versus placebo in time to clinical improvement, 28-day mortality or time to a negative result on a viral RNA test.

The drug was actually numerically worse on 28-day death rates, with 13.9% of recipients dying versus 12.8% on placebo. More than twice as many remdesivir as control patients discontinued treatment because of adverse events – 11.6% in the treatment group versus 5.1% for placebo.

The data came in marked contrast to last week's positive hints from a single site in Gilead's own trial in severe Covid-19 patients, which prompted a major stock rally (*Hospital data leak sets remdesivir expectations, April 17, 2020*).

Hope

Those keeping faith with remdesivir do have some arguments to muster in the drug's favour. Gilead itself stated that the Chinese trial's early termination due to low enrolment – the organisers had intended to recruit 453 patients – meant that the study was underpowered to draw statistically meaningful conclusions.

Certainly underpowering is not an accusation that can be levelled at Gilead's own trial in severe Covid-19: this has been expanded repeatedly, and has now completed enrolment of 6,000 patients.

Another difference between the Chinese study and Gilead's global studies is that patients in the former had been sicker for longer. The Chinese trial recruited subjects whose symptoms had appeared less than 12 days before, while Gilead specified up to four days from confirmation of the presence of coronavirus RNA.

Moreover, Gilead's trial in severe patients excluded subjects who had been mechanically ventilated, or on extracorporeal membrane oxygenation, for at least five days, while this did not apply to the Chinese study.

The general rule with antivirals is that they work best when given fast. According to Umer Raffat of Evercore ISI the timing of treatment initiation is "the most important driver of efficacy"; he called the 12 days post-symptoms criterion in the Chinese trial "a very long window". Leerink analysts echoed this, saying that it was plausible that the negative data could be due to remdesivir being administered too late in the course of illness.

Ultimately these findings, like last week's, are early, incomplete and not yet subject to peer review. Concrete conclusions on remdesivir will only emerge with the full datasets from the large trials – Gilead's pair and the other major study being run by the US National Institute of Allergy and Infectious Diseases – though the latter is not scheduled to report until 2023.

As for Gilead itself, analysts are only now beginning to consider how much remdesivir might mean to the company. Consensus forecasts compiled by *EvaluatePharma* put 2021 sales at $1.4bn.

Selected trials of remdesivir

Trial	Description	Location	N	Results
Academic Chinese study (NCT04257656)	Severe disease, vs placebo, quadruple-blind	China	237	Failure
Academic Chinese study (NCT04252664)	Mild and moderate disease, vs placebo, quadruple-blind	China	308	Expected end of April
Gilead trial (NCT04292899)	Severe disease, uncontrolled	Global	6,000	Expected end of April
Gilead trial (NCT04292730)	Moderate disease, vs standard of care, open-label	Global	1,600	Expected end of May

Source: EvaluatePharma, clinicaltrials.gov.