Evaluate Vantage

March 12, 2014

FDA’s left-field shot crushes Geron

Jacob Plieth

Just when it seemed that Geron’s biggest worry with developing imetelstat was myelosuppression, the US FDA has slapped a full clinical hold on the project for a different reason: liver toxicity.

The severe setback punches a hole in plans to develop the agent for myelofibrosis, which had given it and the company a new lease of life. Investors now await confirmation of how long the delay will last, though judging by the market reaction – Geron stock opened down 65% this morning – chances of a swift resolution are seen as slim.

The immediate effect of the FDA’s verbal notice is that all ongoing imetelstat trials have to be stopped. This includes the company’s phase II studies in essential thrombocythaemia or polycythaemia vera and multiple myeloma, and will surely also hit the Mayo Clinic’s myelofibrosis trial.

It was the Mayo study, run by the controversial myelofibrosis expert Dr Ayalew Tefferi, that had caused a surge of investor interest in Geron, prompting the company’s stock to climb fourfold last year in the run-up to December’s ASH conference.

Of course, ASH turned out to be a damp squib for Geron, with doubts setting in about the criteria Dr Tefferi had used to define remission, and concerns voiced about imetelstat’s safety. Severe myelosuppression had been seen in an intensive-dosing arm, and there were two patient deaths (*ASH – Interesting theories, but doubts on novel myelofibrosis projects remain, December 11, 2013*).

Unexpected?

As such, the FDA’s focus on persistent low-grade liver function test abnormalities and the risk of chronic liver injury after long-term exposure to imetelstat might come as a surprise.

Still, on a call today Geron confirmed that it had seen persistent liver abnormalities in trials, and indeed a phase II study in essential thrombocythaemia had shown 90% of patients exhibit liver enzyme elevations. But an independent panel of experts had reviewed the data and decided that the risk/benefit was favourable.

Acute elevations did resolve, the company said, but it is not these but rather the persistent, low-grade liver function abnormalities that concern the FDA. The agency in particular wants to see data on whether these low-grade effects are reversible, presumably with lower dosing.

There has been no confirmation as to the effect of the hold on Dr Tefferi’s study, but it must be assumed that this too will be stopped. Recruitment into this trial was halted in January – a decision Geron said had nothing to do with liver function test abnormalities.

While the setback came as a surprise to Geron, analysts at UBS, who cover its myelofibrosis competitor Incyte, said they had previously noted that imetelstat data had shown significant toxicity. The only visible competition to Incyte’s Jakafi was now Gilead’s momelotinib, they wrote today (*Therapeutic focus – New agents nip at Jakafi’s heels in myelofibrosis, October 1, 2013*).

Resolution

Geron refused to comment on how long the hold would take to be lifted, but said it would address the issues once it received a formal letter from the FDA. UBS said a near-term resolution appeared “unlikely”.

Thanks to the buzz around Dr Tefferi’s study Geron was able to raise $97m in February, and said it would run its own phase II study of imetelstat in myelofibrosis. This was to have started in the first half of this year, but will clearly not begin while the US hold is in place.

With the company now worth a mere $240m, a healthy cash position is one of its few remaining positives. It might be cold comfort, but Geron will be thankful that it managed to raise the money when it did.

Active imetelstat trials			
Study	**Sponsor**	**Status**	**Trial ID**
Ph II, brain tumours, 110 patients	Pediatric Brain Tumor Consortium	Recruiting	NCT01836549
Ph II, myelofibrosis, 40 patients	Mayo Clinic	Ongoing, recruitment closed	NCT01731951
Ph II, multiple myeloma, 48 patients	Geron	Ongoing, recruitment closed	NCT01242930
Ph II, essential thrombocythemia/polycythemia vera, 40 pts	Geron	Ongoing, recruitment closed	NCT01243073
Ph I, Her2+ breast cancer, 10 patients	Indiana University	Ongoing, recruitment closed	NCT01265927

To contact the writer of this story email Jacob Plieth in London at jacobp@epvantage.com or follow @JacobEPVantage on Twitter