Evaluate Vantage

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Upcoming events: Antidote data from Portola and US action on Actavis antibiotic

Joanne Fagg

Welcome to your weekly digest of approaching regulatory and clinical readouts. Further data from Portola's factor Xa inhibitor antidote are expected in the coming months. With positive results for andexanet alfa against Eliquis and Xarelto already, Portola is in a strong position that could see the buyers come knocking.

Meanwhile an FDA decision on Actavis and AstraZeneca's ceftazidime-avibactam, which targets Gram-negative bacteria, is expected in the first quarter. An FDA adcom at the end of last year was mixed, recommending approval in certain settings and not others.

Andexanet alfa: Portola Pharmaceuticals

The phase III Annexa-A study yielded positive results at the end of last year. Data from the first part of the study, in 33 healthy volunteers 50-75 years old, showed that andexanet alfa reversed the anticoagulant activity of Eliquis by approximately 94%, with a p value of less than 0.0001 versus placebo. Portola shares rose 16% (*No bleeding for Portola as factor Xa antidote comes good, October 2, 2014*).

Data from the second part of the study are expected shortly. 32 healthy volunteers were given 5mg of Eliquis and then randomised 3:1 to a 400mg IV bolus of andexanet alfa followed by 4mg a minute for 120 minutes, or placebo.

Trials with additional factor Xa agents also are under way. In January Portola released positive topline data from the first part of their Annexa-R phase III trial testing andexanet alfa with Xarelto in 41 healthy volunteers. Shares climbed 7% on the news. Full results are expected on March 16 at the American College of Cardiology's annual meeting.

The second part of Annexa-R in 40 healthy volunteers, evaluating a bolus plus a continuous infusion of andexanet alfa to sustain reversal, should read out in mid-2015.

Andexanet alfa has breakthrough therapy designation and earlier this year a single-arm phase IV trial started in 270 patients receiving Eliquis, Xarelto or Lovenox who present with an acute major bleed. Data from this trial, plus that from the phase III studies, will serve as the basis for the accelerated approval BLA filing planned for the end of the year.

Portola raised $160m in a share offering after the first results from Annexa-A last year, and boasts cash of $430m. This should be sufficient to fund clinical trials through mid-2016. 2020 sales of andexanet alfa are forecast to reach $343m, according to consensus data from *EvaluatePharma*. With a valuation of $1.3bn and its factor Xa betrixaban also progressing – shares jumped 12% today on news that the pivotal Apex trial passed a final futility test – Portola will be hoping to attract the attention of potential partners.

Ceftazidime-avibactam: (Actavis, AstraZeneca)

In December a FDA panel meeting had a mixed outcome regarding the antibiotic that combines ceftazidime, a third-generation cephalosporin, and avibactam, an anti-beta-lactamase.

The panel voted that ceftazidime-avibactam was safe and effictive when used, in combination with metronidazole, to treat complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI) caused by Gram-negative pathogens.

However, it voted not to recommend the combination for hospital-acquired bacterial pneumonia (HABP), ventilator-associated bacterial pneumonia (VABP) and bacteremia. Panellists did note that if it were approved for cIAI or cUTI physicians might still use it off label for HABP or VABP if their patients had no other options. A final decision by the regulators is expected during the first quarter.

2020 sales are forecast to reach $340m, according to *EvaluatePharma*. AstraZeneca has the rights to ceftazidime-avibactam worldwide except in North America, where they are held by Actavis.

The combination will take a back seat to Zerbaxa, now owned by Merck & Co through its $9.5bn acquisition of Cubist Pharmaceuticals. Zerbaxa is a combination of the beta-lactamase inhibitor tazobactam and ceftolozane, a novel cephalosporin. 2020 forecast sales are expected to reach $735m, according to consensus from *EvaluatePharma*.

Zerbaxa was approved in December for use in cIAI in combination with metronidazole for both Gram-positive and negative bacteria, and cUTI for Gram-negative.

Product	Study	Trial ID
Andexanet alfa	Annexa- A Annexa-R	NCT02207725 NCT02220725

To contact the writer of this story email Joanne Fagg in London at joannef@epvantage.com or follow @JoEPVantage on Twitter