Evaluate Vantage

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Upcoming events – Panel decisions due for Achaogen and Akcea

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Welcome to your weekly digest of approaching regulatory and clinical readouts. Achaogen's antibiotic plazomicin will go before a US advisory committee meeting on May 2 for treating complicated urinary tract infections and bloodstream infections, the latter of which is its main value driver.

Another panel is set for May 10, this time for Ionis's volanesorsen. The antisense project aims to treat a rare hereditary condition characterised by high levels of triglycerides, and safety will be the big topic for discussion as thrombocytopenia was seen in trials.

Plazomicin's label

Achaogen shares rocketed 148% at the end of 2016 when two phase III trials of plazomicin met US and EU primary endpoints.

In the 609-patient Epic trial in complicated urinary tract infections (cUTI) plazomicin showed noninferiority versus meropenem on a prespecified composite of clinical cure and microbiological eradication. The antibiotic was also superior to meropenem on microbiological eradication at the test-of-cure visit. Meropenem is the gold standard treatment for cUTI.

The smaller Care trial, in 69 patients with serious bloodstream infections caused by carbapenem-resistant enterobacteriaceae (CRE), found a lower rate of mortality or serious disease-related complications with plazomicin versus colistin, the standard of care and one of the few remaining antibiotics for this indication *(Epic antibiotic data could spur interest in Achaogen, December 13, 2016).*

Leerink analysts suggest that the major topic of discussion at the panel meeting on May 2 will be labelling – whether or not the Care data in CRE infections are enough to warrant a specific label indication. The Care study was small but showed a large and consistent clinical effect validated by a mortality benefit.

The Epic trial in cUTI will likely support registration, but Leerink models about $300m US sales in 2025 for CRE, against just $140m for cUTI.

Plazomicin was awarded a breakthrough therapy designation for the treatment of bloodstream infections. Whereas historically labelling has been based on infection type, if plazomicin is approved for this use – its PDUFA date is June 25 – it would be the first antibiotic with a pathogen-specific indication.

Study	Trial ID
Care	NCT01970371
Epic	NCT02486627

Safety issues

Volanesorsen is in development for familial chylomicronemia syndrome (FCS) a rare hereditary condition in which patients lack properly functioning lipoprotein lipase, an enzyme that clears triglycerides from plasma. FCS causes repeated episodes of severe abdominal pain and pancreatitis.

Volanesorsen is designed to inhibit the production of apolipoprotein C-III (Apoc-III), a protein that plays a pivotal role in regulating plasma triglycerides. The antisense project is being developed by the Ionis subsidiary Akcea, which will commercialise it if it is approved.

An advisory meeting is scheduled for May 10, with a PDUFA date set for the end of August. The drug was filed on the basis of the pivotal Approach study in 66 FCS subjects and the Compass trial in 113 patients with very high triglycerides.

Approach showed a 77% mean reduction in triglycerides at three months, while the number in Compass was

71%. Both studies also demonstrated a statistically significant reduction in pancreatitis attacks *(Snippet roundup: Acorda wins, Ionis loses – maybe, March 10, 2017).*

The big issue for the FDA panel will be safety – three patients experienced grade 4 thrombocytopenia during the Approach trial, which led to the implementation of platelet monitoring. Despite this monitoring another case was disclosed earlier this year in an FCS open-label extension study, causing Akcea's shares to fall 26%.

The platelet reductions appear to be inversely correlated to patient weight – the lighter the patient the more prone they are to thrombocytopenia. On its recent earnings call Akcea noted that the data still supported a once-weekly 300mg volanesorsen dose, but that the company also expected to enact weight-based dosing adjustments, with dosing potentially adjusted to every two weeks.

As the proposed dosing programme differs from that of the fixed-dose regimen used in Approach the FDA could request additional dosing work before approval, and also require stringent monitoring protocols.

Study	**Trial ID**
Compass	NCT02300233
Approach	NCT02211209
Approach extension study	NCT02658175

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