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# Upcoming events – Karyopharm's myeloma expansion and Pfizer's biz dev nous

Joanne Fagg

**Karyopharm hopes to move Xpovio earlier in the multiple myeloma treatment sequence, and data are due for Akcea/Ionis's triglyceride regulator, for which Pfizer paid a hefty sum.**

Welcome to your weekly roundup of approaching clinical readouts. In July Karopharm's Xpovio was approved for multiple myeloma on the basis of the phase II Storm trial, but in a tiny, last-chance setting (*Karyopharm rollercoaster ends in selinexor approval, July 4, 2019*). The upcoming readout of a phase III study, Boston, in earlier lines of treatment, could allow the drug's expansion into a much larger population.

Boston is testing the XPO1 inhibitor in adults with relapsing-remitting multiple myeloma who have received one, two or three prior regimens. There are around 23,000 such patients in the US, according to Leerink analysts. The population in which Xpovio is already approved – patients refractory to at least two proteasome inhibitors, at least two immunomodulatory drugs, and an anti-CD38 MAb – amounts to around 7,000.

Boston has enrolled 400 subjects and pits Xpovio plus Velcade and dexamethasone against a control group given the latter two compounds. Control patients can cross over into the Xpovio combo arm if objective disease progression is confirmed.

The primary endpoint is progression-free survival at 15 months, but toxicity will also be a major focus. In Storm 9% of the patients had fatal adverse events, but approval came anyway since the setting was so intractable. In earlier lines of therapy this justification will be harder to use.

If Boston hits, Leerink thinks it could add $123m to Xpovio's US sales in 2028. Sellside consensus compiled by *EvaluatePharma* forecasts 2024 worldwide revenue for Xpovio of $584m, though this also includes sales in non-Hodgkin lymphoma and soft tissue sarcoma.

But there is a risk here too: if Boston shows the product's safety profile to be markedly worse than expected, the approval granted in July could be withdrawn. This would be a highly unusual step for the FDA, particularly given its recent positive inclinations, but cannot be ruled out entirely.

**Worth it?**

Meanwhile, Pfizer will shortly find out whether the $250m it spent on Akcea/Ionis's AKCEA-ANGPTL3-LRx was worth it. A proof-of-concept phase II trial  in 144 subjects with type 2 diabetes, high triglycerides or non-

alcoholic fatty liver disease will soon yield data.

The project is a ligand-conjugated antisense oligonucleotide that aims to reduce production in the liver of angiopoietin-like 3 protein (ANGPTL3), a key regulator of triglycerides, cholesterol, glucose and energy metabolism. Elevated levels of the protein are associated with an increased risk of heart attacks, thickening of the arterial walls and multiple metabolic disorders.

The phase II study is testing three subcutaneous doses of AKCEA-ANGPTL3-LRx versus placebo, and the primary endpoint is the percentage change in fasting triglycerides from baseline to month six, with secondary endpoints including change in liver fat.

In a phase I/II study the project demonstrated a dose-dependent reduction in ANGPTL3 of 84.5% at the highest dose, with a concomitant decrease in triglycerides of 63.1%. There were also reductions in LDL cholesterol and total cholesterol, along with a positive safety profile including no significant platelet count reductions.

When Pfizer bought the rights in October Ionis and Akcea, Ionis's majority-owned subsidiary, shared the up-front fee. Ionis then received $125m in Akcea stock, further increasing its stake in the subsidiary.

Other companies are also interested in ANGPTL3. Regeneron’s evinacumab targets the protein, and a phase III study in homozygous familial hypercholesterolemia showed a 49% reduction in LDL cholesterol from baseline versus placebo. A filing for the antibody is expected by mid-2020.

Also Arrowhead’s ARO-ANG3, an RNAi therapy, has phase I/II healthy volunteer data showing a mean maximum reduction from baseline of 66% in triglycerides and 30% in LDL-C at a single dose. Data from the multi-dose cohort in patients with non-alcoholic fatty liver disease, hyperlipidemia while on statins, familial hypercholesterolemia and severe hypertriglyceridemia are expected this year, with pivotal trials planned.