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Biopharma's Must-Know Q4 Catalysts

by Elizabeth Cairns

Cytokinetics has a lot riding on the upcoming Phase III readout for aficamten, and crunch time is coming for plenty of other groups, too.

The leaves are changing color and the nights drawing in – but what will the final season of the year bring for biopharma? Here, *Scrip* compiles the major clinical readouts that are on the way, and companies including *Sanofi*, *Novartis AG* and *AstraZeneca PLC* stand to gain – or lose.

The table below considers ten products with highly significant clinical readouts coming in the final months of the year. It was constructed by using *BioMedTracker* to identify products with top-line clinical readouts from potentially pivotal trials due in the fourth quarter of this year. The data were then ranked using the assets' forecast 2028 sales, according to *Evaluate Pharma*'s sellside consensus data, and the 10 with the highest forecasts were selected.

Key Takeaways

- Cytokinetics' aficamten has huge sales forecasts, and a hit in Phase III will be a prerequisite for realising these
- Sanofi needs the MS product tolebrutinib to redeem itself
- AstraZeneca is targeting both cancer and COVID

Of all the products identified, *Cytokinetics, Inc.*'s aficamten carries by far the highest expectations for sales five years hence, with sellside analysts expecting it to cross into blockbuster territory in 2027. Only one product is approved for the rare condition aficamten is designed to treat, hypertrophic cardiomyopathy.

This is *Bristol Myers Squibb Company*'s Camzyos (mavacamten), like aficamten a cardiac myosin inhibitor. In its pivotal study, EXPLORER-HCM, significantly more patients treated with Bristol's agent than with placebo responded after 30 weeks' treatment – 37% versus 17%. Response was defined as achieving either improvement of mixed venous oxygen tension (pVO2) by at least

1.5mL/kg/min plus improvement in NYHA class by at least one, or improvement of pVO2 by at least 3mL/kg/min plus no worsening in NYHA class.

The primary endpoint of aficamten's pivotal study, SEQUOIA-HCM, is simpler: change in pVO2 at 24 weeks, compared with placebo. The proportion of patients whose NYHA class improves by at least one will be assessed as a secondary endpoint.

Analysts from Truist Securities, in a note dated 10 September, wrote that they believed that SEQUOIA-HCM was likely to show aficamten to be comparable to Camzyos on efficacy, with potential for better safety. Not that safety was a particular worry with Camzyos – EXPLORER-HCM threw up no major concerns, with rates of treatment-emergent adverse events and serious cardiac adverse events being similar in the two arms.

But Cytokinetics is way behind Bristol. Camzyos was launched in 2022, and has 2028 sales forecasts of $1.9bn in hypertrophic cardiomyopathy. Still, aficamten is unpartnered; should the pivotal SEQUOIA trial be toplined a hit, Cytokinetics can expect interested parties to make themselves known, and if enough marketing muscle can be brought to bear maybe some ground can be made up.

Corcept Therapeutics Incorporated is also awaiting vital data in a rare disease. Currently, the group has the biggest-selling Cushing's disease therapy, Korlym (mifepristone), but this was first approved in 2012 and sales are forecast to start dwindling soon.

Corcept is thus banking on its next-generation version relacorilant, which, like Korlym, achieves its effect by competing with cortisol at the glucocorticoid receptor. Unlike Korlym, relacorilant does not bind to the progesterone receptor, and so does not cause progesterone receptor-mediated side effects, including termination of pregnancy, endometrial thickening and vaginal bleeding. Neither does it cause hypokalemia, the serious side effect experienced by 44% of patients in Korlym's pivotal trial. Korlym-induced hypokalemia is a leading cause of Korlym discontinuation.

The company also says that relacorilant has no effects on the heart's QT interval, meaning it could become the only drug in Cushing's syndrome that does not have this side-effect.

Relacorilant is in two Phase III trials: GRACE, studying the product's effectiveness and safety in patients with endogenous Cushing's disease, which is intended to be registrational; and GRADIENT looking at relacorilant in treating cortisol-secreting adrenal adenomas or hyperplasia.

The two studies are on track to report top-line data towards the end of 2023 or in the first quarter of 2024, and safety in particular will be scrutinised closely. Should the trials turn out positive,

data from both will be included in the company's planned NDA submission, targeted for the first half of 2024. The sellside currently forecasts that the next-generation product will become the new bestselling Cushing's therapy in 2026.

Intolebrutinib

Sanofi's multiple sclerosis candidate tolebrutinib has not had an easy development path, but two trials set to read out soon could allow the French company to garner some sales from the product. In July 2022, the US Food and Drug Administration put a partial clinical hold on tolebrutinib, preventing the recruitment of new patients in Phase III trials. The MS trial affected was PERSEUS, for the primary progressive form of the disease (Also see "*Sanofi's MS Candidate Tolebrutinib On Clinical Hold Following Liver Toxicities*" - Scrip, 30 Jun, 2022.).

Fortunately, two Phase III trials in relapsing MS were already fully enrolled, and were thus permitted to continue. The identical GEMINI 1 and 2 studies are comparing tolebrutinib with Sanofi's older oral MS drug Aubagio (teriflunomide), which fell to generic competition earlier this year.

However, in a note dated 9 August, Cowen analysts wrote that the readouts could be delayed into 2024. Sanofi is measuring disability worsening or disease progression, which needs to be confirmed for at least six months, but has said it is seeing fewer events than anticipated.

The analysts added that Sanofi believed that drug-induced liver events that led to the partial clinical hold were a class effect of BTK inhibitors, and that the lack of AEs with some rival BTK blockers is simply a function of insufficient number of patients on drug. Be that as it may, safety will be the main concern for investigators, regulators and patients alike.

LEGENDary

The pivotal trial of *Deciphera Pharmaceuticals, Inc.*'s vimseltinib in the rare disorder tenosynovial giant cell tumor (TGCT) will also read out in the coming quarter, and the company will be hoping for a meaningful improvement over the one product approved for TGCT, *Daiichi Sankyo Co., Ltd.*'s Turalio (pexidartinib).

Tenosynovial giant cell tumors are benign growths that form in the soft tissue around joints. They can grow quickly, and can lead to bone fractures by putting pressure on the bones.

In Turalio's pivotal trial, ENLIVEN, the overall response rate (ORR) at week 25 using RECIST v1.1 was 38% among treated patients and 0% among those given placebo. Conveniently, Deciphera's MOTION study has the same endpoint.

But that is on the efficacy side, and safety is also very much an issue. Turalio's label carries a boxed warning for hepatotoxicity and the drug was rejected by the European Medicines Agency.

Vimseltinib looks cleaner. In Phase II, the most common Grade 3 or worse adverse events were increased liver enzyme levels, but there were no reports of increased bilirubin or other hepatotoxicity events. If MOTION does turn up a hepatotoxicity signal efficacy will need to be very good indeed if Deciphera is to take meaningful share of this small market.

Inventiva S.A.'s NASH product lanifibranor has recently been the subject of a minor licensing deal, an incremental positive as the company heads into the crucial readout of the Phase II LEGEND study. Hepalys Pharma, a new Tokyo-based company created by the venture capital firm Catalys Pacific, has paid $10m upfront to develop and sell lanifibranor in Japan and South Korea.

Interestingly, Inventiva owns 30% of Hepalys, so is in part licensing the drug to itself. Still, the involvement of investors suggests other parties have faith in the PPAR regulator.

Lanifibranor's pivotal trial, NATiV3, will not report for several years; in the interim LEGEND will read out. The trial is comparing the drug with placebo in patients with NASH and type 2 diabetes, but also contains an arm co-administering lanifibranor with Boehringer Ingelheim/Lilly's SGLT2 inhibitor Jardiance (empagliflozin) in the hope of mitigating the weight gain seen in earlier trials. The primary measure is absolute change in HbA1c from baseline to week 24.

Analysts from KBC Securities wrote in a note dated 13 September that the LEGEND data could provide near-term upside for the stock while investors wait for the Phase III results. Since around 37% of NASH patients also have diabetes, positive data could boost lanifibranor's positioning versus the competition (Also see "*A Look Into The Future Of NASH*" - Scrip, 22 Sep, 2023.).

The final three therapies in the table have forecast 2028 sales beneath $300m, but *KalVista Pharmaceuticals Inc*, Novartis and AstraZeneca will still be seeking hits for sebetralstat, atrasentan and AZD3152, respectively.

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