Evaluate Vantage

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Go or no go? The year ends with Covid-19 vaccine approvals in sight

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December promises big US decisions for Novartis, Astrazeneca and Fibrogen, as well as the FDA's first Covid-19 vaccine reviews.

After almost a year grappling with the coronavirus pandemic the most important job for US regulators next month will be reviewing the first Covid-19 vaccines. Biontech and Pfizer's project will be discussed at a panel on December 10, and while a date has yet to be set officially for Moderna to present its candidate a December 17 adcom has been rumoured.

Both vaccines reported impressive topline efficacy earlier this month. The panel hearings should see more granular data, and allow a better assessment of the projects' safety profiles. The FDA is expected to grant both vaccines swift emergency use authorisations.

Apart from Covid-19, the FDA has several important decisions left to make this year, but manufacturing inspection delays owing to pandemic travel restrictions have hit some recent approvals. The issue could extend timelines for Novartis's lipid-lowering project Leqvio, which has a December Pdufa date *(Novartis's big wager on RNAi approaches the finish line, November 25, 2020)*.

Elsewhere, questions remain around Astra and Fibrogen's anaemia pill Evrenzo, due an approval decision by December 20. The novel anaemia treatment demonstrated noninferiority to erythropoiesis-stimulating agents (ESAs) in dialysis-dependent patients, and noninferiority to placebo in non-dialysis patients, across a vast pivotal programme.

However, the developers have been criticised for the way the results were presented, particularly on the critical issue of cardiac safety. Since then, Akebia's vadadustat, like Evrenzo a hypoxia-inducible factor prolyl hydroxylase inhibitor, has been hit by cardiac safety worries, possibly pointing to a class affect. Akebia is pressing on, however, and a filing for the project is expected next year.

The FDA's verdict on Evrenzo is hard to call, though the lack of an advisory committee meeting could increase confidence. A major concern is whether the agency will insist on a black box warning about increased risk of cardiovascular issues, similar to those with ESAs.

At the recent Stifel healthcare conference Fibrogen noted that the impact of a black box warning would likely be modest in dialysis-dependent patients, as ESAs already have a warning. In non-dialysis dependent patients, less than 15% of whom receive anaemia treatment, adoption of Evrenzo could be slower since the perception

of safety would be affected.

Sumitomo’s opportunity

Relugolix’s first pass of the US regulators, in prostate cancer, is due on December 20. The oral GnRH receptor antagonist, trademarked Relumina in Japan, is Myovant’s lead asset. Myovant is already half owned by Sumitomo, and some investors hold out hope that approval will persuade the Japanese company to buy Myovant outright *(Sumitomo takes out Urovant, and Myovant beckons, November 13, 2020).*

However, questions remain after relugolix's pivotal Hero study produced mixed results. The project met the primary endpoint of testosterone suppression versus leuprolide, the established androgen-deprivation therapy, but also failed to show superiority in castration resistance-free survival.

Supporters of the stock were keen to point out that the superiority endpoint was a secondary measure, and relugolix beat leuprolide on safety, showing a 54% lower risk of major adverse cardiovascular events.

Investors will have to wait until the middle of next year for relugolix’s Pdufa in uterine fibroids, the project’s most lucrative indication. Over half of the drug’s $721m forecast 2026 sales are assigned to uterine fibroids, with just $174m in prostate cancer and the remainder in endometriosis, where the project is in phase III.

Behind the competition

Macrogenics’ margetuximab has a decision date of December 18 but the Her2-targeting antibody has struggled to outshine rivals. Data from the Sophia trial in third and fourth-line Her2-positive metastatic breast cancer showed an ORR of just 22.1%, and there was no survival benefit over Herceptin. A final OS analysis of Sophia is due in the second half of next year.

Astrazeneca and Daiichi’s antibody-drug conjugate Enhertu was granted accelerated approval last December after showing a 60.3% response rate in heavily pretreated breast cancer patients. These companies are now going after earlier settings, and the ongoing Destiny-Breast 02 study pits Enhertu against Herceptin and chemotherapy in those who have progressed on Roche's Kadcyla.

Consensus sales forecasts show which project sellside analysts are backing: margetuximab is expected to hit $277m in breast cancer sales by 2026 versus Enhertu’s blockbuster-level forecast of $3.5bn.

The tables below list first-time and supplementary US approvals as well as panel meetings due next month, with consensus forecasts from *EvaluatePharma*.

Advisory committee meetings in December				
Project	**Company**	**Adcom date**	**2026e sales by indication ($m)**	**Note**
BNT162b2	Pfizer/Biontech	Dec 10	609	Covid-19 vaccine
Entresto	Novartis	Dec 15	4,030*	sNDA for heart failure with preserved ejection fraction
**SBI data not split out. Source: FDA adcom calendar & EvaluatePharma.*				

Notable first-time US approval decisions due in December				
Project	**Company**	**PDUFA date**	**2026e sales by indication ($m)**	**Note**
Leqvio (inclisiran)	Novartis	Dec	2,008	*Novartis's big wager on RNAi approaches the finish line*
Brixadi	Camurus/ Braeburn	Dec 1 (resubmission)	-	Treatment of opioid use disorder
Orladeyo (berotralstat)	Biocryst	Dec 3	382	Prevention of hereditary angioedema attacks
Margetuximab	Macrogenics	Dec 18	277	See text
Relugolix	Myovant	Dec 20	174	See text
Evrenzo (roxadustat)	Astrazeneca/ Fibrogen/ Astellas	Dec 20	1,845	See text
Vibegron	Urovant (Sumitomo Dainippon)	Dec 26	425	Overactive bladder
Ontinua ER (arbaclofen)	Osmotica	Dec 29 (resubmission)	64	MS spasticity
Furoscix	Scpharmaceuticals	Dec 30 (resubmission)	-	Worsening heart failure due to congestion
Tirbanibulin ointment (KX2-391/KX-01 ointment/ALM14789)	Athenex/Almirall	Dec 30	133	Actinic keratosis
Dostarlimab	GSK	By YE	571	Anti-PD-1 filed in endometrial cancer
Sources: EvaluatePharma & company releases.				

Supplementary and other notable approval decisions in December			
Product	**Company**	**Indication (clinical trial)**	**Date**
Bijuva	Therapeuticsmd	0.5mg/100mg dose for menopause (Replenish)	Estimated December
Hetlioz	Vanda	Hetlioz capsules and liquid formulation used to treat Smith-Magenis Syndrome (pivotal Ph2/3 data)	Dec 1
Ocrevus	Roche	Two-hour infusion , dosed twice yearly for relapsing or primary progressive MS (Ensemble Plus)	Dec 14
ABP 798 (Rituxan biosimilar)	Amgen/ Abbvie	CD20-positive B-cell NHL, CLL, RA (NCT02792699, Jasmine)	Dec 19
Krabeva/MYL-1402O (Avastin biosimilar)	Biocon/ Mylan	1L and 2L met colorectal cancer (+ fluorouracil-based chemo); 1L non-squamous NSCLC; recurrent glioblastoma; met renal cell carcinoma (+ interferon alfa); and persistent, recurrent or met cervical cancer	Dec 27
Trikafta, Symdeko, Kalydeco	Vertex	To include additional rare CFTR mutations in cystic fibrosis (based on in vitro data)	Dec 30
Xolair	Novartis/ Roche	Nasal polyps (Polyp 1 and 2)	Q4
Sources: EvaluatePharma & company releases.			