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20 Jul 2023 | **Analysis**

10 Approvals To Look Out For In Q3 2023

by Alex Shimmings

The third quarter could bring US approvals for a range of novel drugs, including the first treatment for a common eye disease, the first US approval of PD-1/L1 inhibitor from a Chinese firm, and the first oral therapy for postpartum depression.

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Daiichi Sankyo's Quizartinib

PDUFA for NDA - Second Review 24 July

Despite launching the product as Vanflyta in 2019, *Daiichi Sankyo Co., Ltd.* has been waiting a long time for US approval of quizartinib, its oral FLT3 kinase inhibitor, for the treatment of adult patients with FLT3-ITD acute myeloid leukemia (AML), which could finally come later this month.

An original 2018 Food and Drug Administration priority review filing, based on the pivotal Phase III QuANTUM-R study of the drug as a single agent in the relapsed/refractory setting, met with a rebuff from the agency's Oncologic Drugs Advisory Committee, which decided that the underwhelming 1.5 month benefit in overall survival (OS) seen in the trial did not outweigh the safety risks, and asked for another study.

A Complete Response Letter and a negative opinion from the EU's CHMP followed, as did Daiichi's second pivotal Phase III trial, QuANTUM-First, which proved much more convincing. QuANTUM-First tested quizartinib this time in combination with chemotherapy in newly diagnosed patients and showed a median OS of more than double at 31.9 months for patients receiving quizartinib compared with 15.1 months for those on chemotherapy alone, after a median follow-up of 39.2 months.

Daiichi's resubmitted NDA for quizartinib for use in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, and as continuation monotherapy following consolidation, was again granted a priority review, but in April the company faced a three-month delay while the FDA reviewed updates it had requested for a risk evaluation and mitigation strategy (REMS).

Despite the repeated setbacks, if quizartinib does wins the agency's nod, it could find itself in a competitive position.

Long Road For Daiichi Sankyo's Quizartinib Gets Longer As FDA Extends Review Time

By Alaric DeArment

21 Apr 2023

The drug could nevertheless find itself in a competitive position if approved for frontline FLT3-ITD acute myeloid leukemia, especially as competitor Astellas's Xospata has repeatedly stumbled.

Read the full article here

It will go up against two marketed FLT3 inhibitors for AML, *Astellas Pharma, Inc.*'s Xospata (gilteritinib), and the first drug in the class, *Novartis AG*'s Rydapt (midostaurin). Rydapt is

approved for newly diagnosed FLT3-positive AML in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation.

While Rydapt's approval is for a broader FLT3-mutated population, its label does include data in FLT3-ITD AML from the pivotal Phase III trial of the drug, Study 1, meaning quizartinib could become its nearest competitor, but with more specific labeling for FLT3-ITD and a post-consolidation monotherapy indication.

Xospata's approval, meanwhile, is as a monotherapy for relapsed/refractory FLT3-positive AML and Astellas has struggled to expand its label beyond the relapsed/refractory population. (Also see "*Astellas' Phase III Front-Line AML Study Of Xospata Fails*" - Scrip, 21 Dec, 2020.)

FLT3-ITD (internal tandem duplication) is the most common type of FLT3 mutation in AML, occurring in about 25% of all newly diagnosed patients, and is associated with increased risk of relapse and shorter overall survival.

Analysts at Credit Suisse believe AML could become a >$10bn market over the next decade. While no AML drug has hit $1bn in sales to date, they said in a research note last year, worldwide estimates predict AML drug sales to grow from $1.3bn in 2021 to $10.5bn in 2028, driven by new modalities and renewed interest.

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Coherus BioSciences' Toripalimab

PDUFA for BLA - Second Review July-September

If successful at the FDA this quarter for use in nasopharyngeal cancer, toripalimab will be *Coherus BioSciences, Inc.*'s first approved treatment in the US. The PD-1 inhibitor is the lead of three drugs from the Chinese firm currently in development for the US market.

Toripalimab is the firm's key pipeline asset as a potentially best-in-class checkpoint inhibitor with a differentiated MOA and potential as backbone checkpoint inhibitor of choice in combination therapies across multiple indications, especially metastatic prostate

Transforming Coherus Adds To IO Pipeline Via Merger With Surface Oncology

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cancer, said analysts at Truist in a 1 May note.

Upon binding with its specific antigen PD-1 receptor, toripalimab blocks the interaction of PD-1 and its ligand and simultaneously induces the internalization of the PD-1 receptor and decreases the expression of PD-1 on the cell membrane surface. Additionally, the binding of toripalimab to PD-1 is independent of glycosylation modifications of PD-1, which play a role in the development a progression of multiple tumors.

By Joseph Haas

16 Jun 2023
Currently battling AbbVie over pricing plans for its Humira biosimilar, Coherus is also looking to become an immuno-oncology player, acquiring two more clinical assets in an all-stock deal.

Read the full article here

It was first approved in China for the treatment of melanoma in 2018, and since then has received five further indications there.

In the US, the FDA is evaluating toripalimab for the treatment of recurrent or metastatic nasopharyngeal carcinoma in combination with chemotherapy, an indication for which there are no other approved therapies for this indication.

The drug is currently in clinical development in the US for multiple cancer indications, and has FDA breakthrough therapy designation and orphan drug status for nasopharyngeal cancer.

Coherus has already studied toripalimab in two clinical studies in China including the Phase III JUPITER-02 study comparing toripalimab plus chemotherapy versus placebo and chemotherapy for recurrent or metastatic nasopharyngeal cancer. However, a rolling BLA based on this study received a complete response letter in March 2021 requesting a quality process change.

Further delays came when COVID-19 pandemic travel restrictions hindered the completion of onsite inspections following resubmission of the BLA.

As of May 2023, the FDA had completed the required pre-licensing inspection of the manufacturing site in China, and Coherus continues to collaborate with the agency to complete all clinical site inspections. The company expects an approval decision in the third quarter of 2023.

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Sage Therapeutics' Zuranolone

PDUFA for NDA - First Review 5 August

As there are currently no oral therapies specifically approved for post-partum depression (PPD), if approved, *Sage Therapeutics, Inc.* and *Biogen, Inc.*'s zuranolone (previously SAGE-217) would address an unmet need there, while also providing an alternative for the treatment of major depressive disorder (MDD).

Zuranolone, which is given once-daily for 14 days, is an oral neuroactive steroid GABA-A receptor positive allosteric modulator that targets brain networks responsible for functions such as mood, arousal, behavior and cognition to help rebalance dysregulated neuronal networks.

Even if all goes to plan in the priority review, it will be late 2023 before zuranolone is available for patients because the neuroactive steroid drug will require Drug Enforcement Administration scheduling, which will take about three months. However, that will give the Sage and Biogen sales teams more time to continue conversations with patients, physicians and payers about the new type of treatment they hope to bring to market. (Also see "*Zuranolone Launch Requires Sage To Shift The Way Doctors Treat Depression*" - Scrip, 21 Feb, 2023.) Sage already markets the injectable drug Zulresso (brexanolone), for PPD.

The NDA submission included data from the LANDSCAPE and NEST development programs for zuranolone in MDD and PPD, respectively.

NEST included two studies in PPD, dubbed ROBIN and SKYLARK. The Phase III SKYLARK trial achieved the primary and all key secondary endpoints, showing a statistically significant and clinically meaningful improvement in depressive symptoms at day 15 as determined by the HAMD-17 scale.

Additionally, the trial demonstrated that a higher proportion of PPD patients in the zuranolone 50mg arm achieved a HAMD-17 response (≥ 50% decrease from baseline HAMD-17 total score) compared with the placebo arm at days 3, 8, 15, 21, and 28. In all clinical development programs so far, zuranolone was generally well tolerated, with a consistent safety profile.

The FDA has granted breakthrough therapy designation and fast-track designation for zuranolone in MDD.

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Galera Therapeutics' Avasopasem Manganese

PDUFA for NDA - First Review 9 August

Galera Therapeutics, Inc.'s selective dismutase mimetic candidate, avasopasem manganese (GC4419), has already earned a breakthrough therapy designation from the FDA for its intended indication to reduce radiotherapy-induced severe oral mucositis (SOM) in head and neck cancer patients and is now advancing toward a 9 August priority review PDUFA goal date.

An approval from the FDA would mean avasopasem manganese would be the first new therapy for mucositis in almost two decades, since the approval of *Swedish Orphan Biovitrum AB*'s Kepivance (palifermin) in 2004.

Avasopasem reduces elevated levels of superoxide caused by radiation therapy by converting superoxide to hydrogen peroxide and oxygen.

In the Phase III ROMAN study, avasopasem demonstrated a significant 16% relative reduction in the primary endpoint of reduction in the incidence of SOM as well as a significant 56% relative reduction in the number of days of SOM, with a median of 18 days in the placebo arm compared with eight days in the avasopasem arm.

In June 2023, Galera presented data from the ROMAN trial at the American Society of Clinical Oncology meeting that showed that avasopasem was linked with significant improvements in preservation of kidney function compared with placebo and resulted in a reduction of cisplatin-related chronic kidney disease.

These results indicate that avasopasem's effect could go beyond head and neck cancer and possibly have an impact on platinum-containing regimens in other cancers.

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Regeneron Pharmaceuticals' Pozelimab

PDUFA for BLA - First Review 20 August 2023

Regeneron Pharmaceuticals, Inc.'s pozelimab is an investigational, fully human, monoclonal antibody designed to block the activity of complement factor C5 and prevent diseases mediated

by the complement pathway.

It is awaiting US approval for its lead indication, CHAPLE syndrome, for which it has a rare pediatric disease priority review voucher, orphan drug designation, and fast-track designation.

The BLA is supported by results from a Phase II/III open-label trial of pozelimab in 10 patients aged one year or older who were given a single loading dose of pozelimab 30 mg/kg IV on day one, followed by SC weekly weight-based doses of pozelimab. At 24 weeks, the co-primary endpoints were achieved with 100% of patients experiencing rapid and sustained normalization of serum albumin (a disease biomarker) and improvement or no worsening of clinical symptoms.

Analyses of secondary endpoints also showed marked reductions in hospitalization days and total number of albumin transfusions, as well as clinically meaningful increases in body weight for age and stature for age. Adverse events were mild or moderate in severity with the most common being iron deficiency, pyrexia, rhinitis, urticaria and vomiting. None led to treatment discontinuation.

Regeneron is also collaborating with *Alnylam Pharmaceuticals Inc.* to combine use of pozelimab with Alnylam's RNAi drug candidate cemdisiran for paroxysmal nocturnal hemoglobinuria and myasthenia gravis in Phase III trials.

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Astellas/Iveric Bio's Zimura

PDUFA for NDA - First Review 18 August

Another C5 complement inhibitor, this time *Iveric Bio*'s pegylated RNA aptamer Zimura (avacincaptad pegol), is being developed for the treatment of geographic atrophy secondary to age-related macular degeneration (AMD). It was the first and only product to enter clinical trials for Iveric Bio, which has just been acquired by *Astellas Pharma, Inc.*. (Also see "*Astellas Paying $5.9bn For Iveric To Boost Ophthalmology Presence*" - Scrip, 1 May, 2023.)

Zimura was one of the key attractions for the deal announced in May, and one which Astellas said would help offset the erosion of its Pfizer-partnered prostate cancer drug Xtandi (enzalutamide) following the anticipated loss of key patent protections from 2027

Zimura has been granted a breakthrough therapy designation as well as fast-track status from

the FDA.

In October 2019, Zimura met its primary endpoint in reducing the rate of geographic atrophy growth in patients with dry AMD in the pivotal Phase II/III GATHER1 study.

Data from the Phase III GATHER2 study's primary endpoint of rate of growth (slope) in geographic atrophy area over 12 months were also positive, with Zimura 2mg achieving a reduction in the mean rate of growth (slope) for all analyzed subgroups. Additionally, Zimura demonstrated a promising safety profile with no cases of endophthalmitis, intraocular inflammation events, or ischemic optic neuropathy events.

If successful, Zimura will go up against the first approved treatment for geographic atrophy, *Apellis Pharmaceuticals, Inc.*'s Syfovre (intravitreal pegcetacoplan).

Syfovre was only approved by the FDA in the middle of February but has had a strong start on the market. Launched on 1 March, Apellis noted in its first-quarter announcement that the complement C3 inhibitor reached sales of $18.4m. SC148332

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Pfizer's Elranatamab

PDUFA for BLA - First Review August

So far, just one B-cell maturation antigen (BCMA)-directed bispecific antibody, *Johnson & Johnson* and *Genmab A/S*'s Tecvayli (teclistamab-cqyv), has reached the market after it received US FDA accelerated approval in 2022 for multiple myeloma patients with fifth-line and later disease, but several firms are hoping to get a competing drug launched, including *Pfizer Inc.* with elranatamab.

Elranatamab, also a BCMA/CD3-targeted bispecific antibody, is in development for relapsed or refractory multiple myeloma. In January 2021, the FDA granted it fast-track status for multiple myeloma patients who are refractory to at least one proteasome inhibitor, one immunomodulatory drug and one anti-CD38 antibody. It also has a breakthrough therapy designation for relapsed or refractory multiple myeloma, and an orphan drug designation for the treatment of multiple myeloma.

In June 2023, updated results from various ongoing studies presented at the ASCO meeting

showed that elranatamab was effective and well tolerated and no new safety signals were observed. These results further support treatment with elranatamab in patients with relapsed or refractory multiple myeloma post BCMA-directed therapy.

Pfizer is touting elranatamab's potential use in the community oncology setting as an advantage for the product, while another rival *Regeneron Pharmaceuticals, Inc.* hopes to differentiate its candidate, linvoseltamab, from other players on the market and in development on the basis of convenience and low toxicity. (Also see "*Regeneron, Pfizer Tout Potential BCMA Bispecific Advantages At ASCO*" - Scrip, 6 Jun, 2023.)

If approved, elranatamab will be one of 20 approved treatments for multiple myeloma in the US. The product is also awaiting EU approval.

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Tarsus Pharmaceuticals' TP-03

PDUFA for NDA - First Review 25 August

There could be a significant breakthrough in the treatment of Demodex blepharitis if the FDA approves T*Tarsus Pharmaceuticals Inc.*'s TP-03 (lotilaner ophthalmic solution 0.25%), a novel therapeutic developed to specifically target and eliminate Demodex mites, the underlying cause of the condition.

The product is a potent, non-competitive antagonist of insect and arachnid GABA-Cl channels, and also has high lipophilicity, allowing for its effective uptake in the oily sebum of hair follicles in the eyelid margins where the mites live.

There are no treatments currently approved for the condition, and analysts at William Blair predict a bright future for the product as a consequence of its being an effective therapy for a large and motivated patient population.

"With an estimate of 25 million people in the United States, 7 million in the initial target market, and pricing set to range between $1,500 and $2,000 per treatment course, we believe TP-03 is set to become a blockbuster therapy in the eye care segment," they said in a 18 July note. "Given the frankly disgusting pictures of Demodex mite infestation and highly curative nature of TP-03, it is hard to imagine that the marketing of TP-03 will not be more successful than other eye care blockbusters such as dry eye, an indication that is often confused for Demodex blepharitis."

Tarsus Pharmaceuticals' September 2022 NDA included positive results from two pivotal trials, SATURN-1 and SATURN-2, involving over 800 patients.

In SATURN-1, 95% of TP-03 patients showed a significant response in mite count by day 43, achieving ⩽0.5 mites per lash from an average baseline of 3.2 mites per lash, compared with 36% of those on the vehicle (<0.0001).

TP-03 also showed quick efficacy, with 23% of patients achieving a significant cure of collarettes (waxy cuffs encircling the base of the eyelashes) as early as day eight compared to 11% in the vehicle group (p=0.0003). Complete collarette cure (grade 0) at day 43, defined as zero to two collarettes per lid, was achieved by 43% of TP-03 patients versus 7% in the vehicle group (p<0.0001).

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BioLineRx's Aphexda

PDUFA for NDA - First Review 9 September

Approval of Aphexda would signal *BioLineRx Ltd.*'s first approved drug in the US and could provide a much-needed alternative treatment option for stem cell mobilization.

Aphexda (BKT140/motixafortide) is a highly selective inverse agonist of chemokine (C-X-C motif) receptor 4 (CXCR4), with a high affinity and a low rate of dissociation from its receptor. It is being developed by BioLineRx for use in stem cell mobilization for autologous bone marrow transplantation in multiple myeloma patients.

In April, BioLineRx announced data from its Phase III GENESIS trial were published in *Nature Medicine* showing it achieved significance (p <0.0001) across all primary and secondary endpoints. In particular, 92.5% of patients in the one-dose motixafortide plus G-CSF arm achieved the primary endpoint of mobilizing more than 6 million CD34+ cells/kg in up to two apheresis sessions vs 26.2% in the placebo plus G-CSF group. The regimen also had a favourable safety and tolerability profile, and the researchers concluded that the results established significant and clinically meaningful outcomes for the product.

Analysts at Oppenheimer said in a 24 May note that BioLineRx had brought on board an experienced commercial leadership team and a sales force intended to target high-volume US transplant centers and that the *Nature Medicine* publication may help increase product awareness

amongst prescribers ahead of the 9 September PDUFA date. “We believe the company is funded into 1H24—an adequate runway to get Aphexda’s launch off the ground, which can be extended with additional debt tranches as needed.”

“These positive results all bolster the chances of approval of Aphexda which could have a significant impact on the current market,” said analysts at BioMedtracker.

Following any approval and successful US launch, the company hopes to explore ex-US territories with the help from potential partners to commercialize Aphexda.

BioLineRx also continues to progress motixafortide development in pancreatic cancer and stem cell mobilization for gene therapies.

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Novo Nordisk’s Nedosiran

PDUFA for NDA - First Review September

Novo Nordisk A/S is awaiting a decision, due in September, on approval of nedosiran, the lead product from its late 2021 acquisition of *Dicerna Pharmaceuticals, Inc.*. If successful, it will be only the second licensed treatment for primary hyperoxaluria in the US.

Nedosiran uses the GalXC RNAi technology platform and is designed to inhibit the lactate dehydrogenase A (LDHA) enzyme to target primary hyperoxaluria (PH) types 1, 2 and 3. LDHA, believed to be the ultimate step in the oxalate production pathway, was hypothesized to be effective for all three primary hyperoxaluria subtypes, compared with Alnylam’s Oxlumo (lumasiran) which is only approved for PH1.

However, since the acquisition, Novo Nordisk has studied nedosiran in multiple clinical studies, including an open-label, roll-over Phase III study entitled PHYOX3 in patients with primary hyperoxaluria, but data from the trials were mixed, with significant reductions in urinary oxalate in the PH1 subtype but trends toward reductions in PH2 and PH3 subtypes.

For PH1, results from the Phase II PHYOX2 study exhibited a significant reduction in urinary oxalate after treatment with nedosiran, with an overall 57.5% greater daily average reduction compared with placebo.

The FDA has granted nedosiran orphan drug designation for the treatment of primary hyperoxaluria, as well as a breakthrough therapy designation and a rare pediatric designation.

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