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10 Approvals To Look Out For In Q2

by Alex Shimmings

The second quarter has already seen the approval of Gamida Cell's cell therapy Omisirge, and with the help of Biomedtracker, *Scrip* highlights 10 of the more interesting new drug approvals due in the next three months.

Biogen/Ionis's Tofersen For SOD1 ALS

Away from its adventures in Alzheimer's disease, *Biogen Pharma* is hopeful of an accelerated US approval for tofersen, which it licensed from *Ionis Pharmaceuticals, Inc.*, as the first treatment to target a genetic cause of amyotrophic lateral sclerosis (ALS).

On 22 March, the Food and Drug Administration's Peripheral and Central Nervous System Drugs Advisory Committee decided that tofersen was suitable for an accelerated, but not regular, approval as the first disease-modifying treatment for superoxide dismutase 1 (SOD1) ALS, despite it missing the primary endpoint in the Phase III VALOR study. (Also see "*Accelerated Approval Is US FDA Panel's Preferred Path For Biogen/Ionis's Tofersen In ALS*" - Pink Sheet, 22 Mar, 2023.) The product is set to receive an approval decision from the FDA on 25 April.

Tofersen (BIIB067) is an antisense oligonucleotide designed to reduce SOD1 protein synthesis. Mutations in the gene for SOD1 have been associated with about 20% of cases of familial ALS and familial ALS represents about 10% of ALS cases. Patients with SOD1 ALS, estimated to total about 330 in the US, typically have a shorter survival time than those with other forms the rare, fatal neurodegenerative disorder.

VALOR, a six-month pivotal Phase III study in 108 participants, did not meet its

Biogen Prepares More Doubtful Phase III Results For FDA Scrutiny, This Time In ALS

By Andrew McConaghie

23 Sep 2022

After the Aduhelm controversy, Biogen has another neurodegenerative disease drug which so far can only show efficacy against surrogate biomarkers – will the FDA be

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primary endpoint of change from baseline to week 28 in the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale. However, 95 of these patients enrolled in the open-label extension (OLE) study, and combined VALOR and OLE 12-month data showed sustained reductions in SOD1 protein (a marker of target engagement) and neurofilament light chain (NfL, a marker of neurodegeneration).

swayed again this time?

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The committee unanimously agreed that the available evidence was sufficient to conclude that a reduction in plasma NfL concentration in tofersen-treated patients is reasonably likely to predict clinical benefit of tofersen for treatment of patients with SOD1-ALS.

The EMA accepted an approval application for tofersen in December.

GSK's Arexvy And Pfizer's Abrysvo For RSV

A new era beckons for the prevention of respiratory syncytial virus (RSV) with the potential approvals of two vaccines this quarter. These are expected to add to *AstraZeneca PLC* and *Sanofi*'s antibody therapy, Beyfortus (nirsevimab), which was approved last year in the EU for the prevention of the infection in newborns and infants during their first RSV season and is awaiting a similar US approval.

RSV is a highly contagious virus that causes respiratory infections in people of all ages. It is most severe in infants, young children and older adults, and can lead to hospitalization, especially in those with weakened immune systems.

There are currently no RSV vaccines approved in the US, but *Pfizer Inc.*'s Abrysvo and *GSK plc*'s Arexvy are both aimed at preventing the infection in the older (60-years plus) population and both have PDUFA action dates in May, with GSK on track to be the first approved come 3 May.

Pfizer's Abrysvo is based on a prefusion form of the RSV F protein (RSVpreF), while GSK's Arexvy is a recombinant subunit prefusion F glycoprotein antigen (RSVPreF3) combined with its AS01 adjuvant system and a QS-21 Stimulon adjuvant licensed from *Agenus Inc.*

The GSK product had a stronger endorsement in early March from the US FDA's Vaccines and Related Biological Products Advisory Committee although it recommended approval of both vaccines for the prevention of acute respiratory disease and lower respiratory tract disease caused by RSV in adults 60 years of age and older. The committee unanimously voted that GSK's data supported the effectiveness of the vaccine, and 10-2 that the data supported the safety of the vaccine. The margin was much less convincing for Pfizer's candidate the day before, the panel voting 7-4 on safety and by the same margin on effectiveness on 28 February. (Also see

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"*Both Pfizer And GSK RSV Vaccines Set For Approval – But Could Next Readouts Give One The Edge?*" - Scrip, 6 Mar, 2023.)

Both vaccines should be commercially available before the 2023 fall/winter RSV season, putting them at the head of a global market expected eventually to be worth $10bn annually. Such is their expected dominance that *Johnson & Johnson* decided to end development of its Phase III RSV vaccine candidate in late March. (Also see "*J&J Quits RSV Development With Two Rivals Already Poised For US Approval*" - Scrip, 29 Mar, 2023.) Danish firm *Bavarian Nordic A/S*, however, has no such qualms, with a Phase III trial of its candidate progressing well. Its vaccine, MVA-BN RSV, employs five RSV-specific antigens – as opposed to just the F protein – with an aim to stimulate a broad antibody and cellular immune response against both RSV subtypes (A and B). (Also see "*Bavarian Nordic Comes Up On The Rails In RSV Race*" - Scrip, 12 Apr, 2023.)

Chiesi And Protalix BioTherapeutics' Elfabrio

Chiesi Farmaceutici S.p.A. and partner *Protalix BioTherapeutics, Inc.* have a PDUFA action date of 9 May for their resubmitted biologics license application for Elfabrio (pegunigalsidase alfa) for Fabry's disease after the FDA rejected the enzyme replacement therapy in 2021. The product received a European Medicines Agency positive opinion this February.

Elfabrio is a plant cell culture-expressed and chemically modified stabilized version of the recombinant α-Galactosidase-A enzyme, being the first pegylated enzyme for the treatment of adult patients with Fabry's disease.

The company had originally sought an accelerated approval in 2020 based on Phase I/II clinical data and interim clinical data from its Phase III BRIDGE study, as well as safety data from the other Phase III studies that were then ongoing, but the agency's complete response letter cited the COVID-related inability of regulators to inspect its Israeli manufacturing facility and included a request for more data.

In November 2022, the companies resubmitted their BLA to the FDA with a full set of clinical and manufacturing data, including results from all three of Elfabrio's Phase III studies, BALANCE, BRIDGE and BRIGHT. (Also see "*Protalix Plans US Resubmission For ERT For Fabry After Positive Phase III Trial Results*" - Scrip, 4 Apr, 2022.)

If approved, Elfabrio will be one of five approved drugs for Fabry's disease, including those approved outside of the US.

Protalix is counting on Chiesi for the commercialization of the drug, having signed a US commercialization deal in 2018 and one for the European market in 2017.

Byondis's Trastuzumab Duocarmazine

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Another potential antibody-drug conjugate (ADC) from private biopharma firm *Byondis B.V.* is awaiting US and EU approvals following filings made in July 2022 for use in metastatic breast cancer, with a 12 May PDUFA date

Trastuzumab duocarmazine (SYD985) incorporates Netherlands-based Byondis' proprietary duocarmazine linker-drug technology ByonZine. The ADC is comprised of the anti-HER2 monoclonal antibody trastuzumab and a cleavable linker-drug called valine-citrulline-seco-DUocarmycin-hydroxyBenzamide-Azaindole (vc-seco-DUBA). The duocarmycins are potent DNA minor groove binding alkylators, which induce DNA damage resulting in tumor cell death.

The filings were based on results from the Phase III TULIP study in 437 female patients with metastatic breast cancer with a median age of 56 and a median of four prior lines of therapy, which showed significantly improved progression-free survival (PFS) in comparison with standard physician's choice treatment, the primary endpoint. (Also see "*Byondis Seeks Partner For Lead ADC To Enter Crowded Breast Cancer Market*" - Scrip, 9 Jun, 2021.)

SYD985 will face significant competition from other therapies for this treatment setting if approved, with the approvals of *Seagen Inc.* 's Tukysa (tucatinib), Enhertu (trastuzumab deruxtecan), and *MacroGenics, Inc.*c's Margenza (margetuximab) making the heavily pre-treated patient population a crowded space. However, these topline results are an encouraging step forward for Byondis as it seeks approval of the drug.

"While these Phase III results are positive and will likely result in approval in this setting, SYD985's profitable potential is restricted by the progressively crowded third-line market and the company's limited oncology marketing experience and resources in comparison to competitors, particularly Daiichi Sankyo and AstraZeneca," said the Biomedtracker analysts. They added that even though SYD985 showed an advantage over physician's choice of therapy, it was not likely to become the new standard of care over agents with superior efficacy in this setting such as Enhertu and Tukysa.

Like Enhertu, SYD985 has been linked with high rates of interstitial lung disease and treating patients sequentially with each of these agents could lead to higher-grade adverse effects involving lung toxicity. Physicians may be wary about this when treating patients who have previously received Enhertu, which may limit SYD985's uptake, the analysts said.

Innoviva's SUL-DUR

The US Food and Drug Administration's Antimicrobial Drugs Advisory Committee voted 12-0 on 17 April that the overall benefit-risk assessment is favorable for the use of Innoviva subsidiary Entasis's antibacterial combination sulbactam-durlobactam (SUL-DUR), although not for the precise indication the company had originally wanted.

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Initially, Entasis was aiming to get the drug approved for a pathogen-specific, not site-specific, indication, namely for the treatment of infections due to *Acinetobacter baumannii-calcoaceticus* (ABC) ABC complex including multidrug-resistant and carbapenem-resistant strains, but the indication was changed after FDA put out its initial advisory committee meeting notification. Neither the company nor the FDA have addressed why this shift occurred. (Also see "*Entasis Antibiotic Indication Changed Ahead Of FDA Panel, Ending Quest For First Pathogen-Specific Approval*" - Pink Sheet, 13 Apr, 2023.)

The result was that the panel gave it the thumbs up for use in a narrower setting: hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia caused by susceptible strains of ABC organisms. (Also see "*FDA Advisors Give Entasis Antibiotic Unanimous Thumbs Up, But Call For Strong Postmarket Surveillance*" - Pink Sheet, 17 Apr, 2023.)

The filing for the combination therapy received a priority review voucher in November 2022, and the PDUFA date is set for 29 May.

Acinetobacter species are innately resistant to many classes of antibiotics, including penicillin, chloramphenicol and often aminoglycosides, and are associated with high morbidity and mortality rates, creating an urgent need for effective treatments. This need is reflected in the product's fast track and qualified infectious disease product designations.

Entasis projects that there are between 16,000 and 30,000 ABC infection cases a year and about 40% of those are carbapenem-resistant. Mortality rate estimates for treatment-resistant ABC infections range broadly but are thought to sit between 40%-50% although outside estimates put the mortality risk as high as 80%.

SUL-DUR was non-inferior to colistin in a Phase III study of 177 adults, who were also treated with imipenem background therapy. SUL-DUR demonstrated lower mortality, higher clinical cure rates and greater microbiologically favorable outcomes compared with colistin. All-cause mortality at day 28 was 19% in the SUL-DUR group and 32.3% in the colistin group.

Previously, the company also noted that SUL-DUR offers a better nephrotoxicity safety profile versus colistin. Analysts at Morgan Stanley have forecasted sales of $90m-$110m in 2030 for the product.

Sarepta Therapeutics/Roche's SRP-9001

Controversy seems never far away from *Sarepta Therapeutics, Inc.*'s FDA filings and that for its investigational gene therapy for Duchenne muscular dystrophy (DMD), SRP-9001 (delandistrogene moxeparvovec) is proving no exception.

On 16 March, Sarepta announced that the agency had determined that an advisory committee

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meeting would be held for SRP-9001 after all in advance of its PDUFA date of 29 May.

Just a few weeks before, the US regulator indicated to the company that it would not require an AdComm input on SRP-9001, opening up a clear run towards the FDA's PDUFA decision date of 29 May. (Also see "*No AdComm Puts Sarepta On Path To Blockbuster Success With Duchenne Gene Therapy*" - Scrip, 1 Mar, 2023.)

However, it recently transpired that the decision to file the product in the first place was taken against the wishes of the agency's reviewers and was prompted by the CBER Director Peter Marks who was apparently concerned about public opinion and the reactions of advocates and others if the application was refused. (Also see "*CBER Director Marks' Intervention On Sarepta Gene Therapy Filing Decision Appears To Backfire*" - Pink Sheet, 15 Apr, 2023.)

As a result, the upcoming panel meeting on 12 May could now involve as much scrutiny of the agency as the application itself, but it is expected to focus on whether the increase in dystrophin production seen with the gene therapy is reasonably likely to predict clinical benefit in DMD.

In September 2022, Sarepta submitted a BLA to the US FDA for the accelerated approval of SRP-9001 to treat ambulant patients with DMD based on preclinical, biomarker and clinical functional results. The company has studied SRP-9001 in several trials including the Phase Ib ENDEAVOR study, a Phase I/IIa study, a Phase II study, the Phase III EMBARK study, and has planned the Phase III ENVISION and ENVOL studies.

Sarepta's recently fully enrolled Phase III EMBARK study has been proposed to serve as the post-marketing confirmatory study to support any accelerated approval.

This is not the first time Sarepta has appeared to benefit from the intervention of a center director. When the agency reviewed the application for the firm's DMD treatment Exondys 51 (eteplirsen), the review team was against approval. But then-Center for Drug Evaluation and Research Director Janet Woodcock overruled them and granted an accelerated approval.

If SRP-9001 is given the nod, this will be Sarepta's fourth approval in the DMD indication and it will become one of six drugs approved for these patients. It is expected to put some commercial pressure on the nucleic-acid based drugs.

Pfizer's Ritlecitinib For Alopecia Areata

Pfizer is hoping to go up against *Eli Lilly and Company* in the increasingly competitive area of alopecia areata with its small-molecule JAK3 inhibitor ritlecitinib. The FDA is expected to make a decision in the second quarter of 2023 (the drug has breakthrough therapy status) and the EMA in the fourth quarter of 2023, following September 2022 filings, and regulatory decisions are also pending in the UK, Japan and China.

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The submissions are based on the pivotal Phase IIb/III ALLEGRO study in 718 adult and adolescent alopecia areata subjects with 50% or greater scalp hair loss, in which patients who received 50mg or 30mg ritlecitinib (with or without one month of initial loading dose treatment of once-daily ritlecitinib 200mg), achieved the primary efficacy endpoint of proportion of patients with scalp hair regrowth, based on an absolute Severity of Alopecia Tool (SALT) Score ⩽20 at week 24. These positive data put ritlecitinib in the running to potentially compete with Eli Lilly's JAK1/2 inhibitor Olumiant (baricitinib), which demonstrated around a 30% placebo-adjusted improvement in the proportion of patients reaching 80% or greater scalp hair coverage after 36 weeks of 4mg/day treatment. (Also see "*Lilly's Olumiant Is First Drug FDA Approved For Alopecia Areata*" - Scrip, 13 Jun, 2022.)

Like all other JAK inhibitors on the market, Olumiant's label carries a black box warning for serious infections, lymphoma and thrombosis, which could be a potential barrier to uptake. In the ALLEGRO trial, the most common adverse events observed with ritlecitinib treatment were nasopharyngitis, headache, and upper respiratory infection and there were no major adverse cardiac events, deaths, or opportunistic infections. However, ritlecitinib may also have this safety warning if it is approved, as this drug falls into the same class as Olumiant, note the Biomedtracker analysts.

A possible third-to-market JAK inhibitor for alopecia areata is *Concert Pharmaceuticals, Inc.*'s deuterated formulation of ruxolitinib. The US biotech firm was acquired in March by India's *Sun Pharmaceutical Industries Ltd.* which wanted to add the drug to its dermatology portfolio. (Also see "*Sun Pharma Will Take Concert's Alopecia Drug The Rest Of The Way*" - Scrip, 19 Jan, 2023.) (Also see "*Sun Eyes Big Stage For Concert's Alopecia Asset*" - Scrip, 10 Feb, 2023.)

GSK's Momelotinib For Myelofibrosis

Another one of a number of expected approvals for GSK this year is for its oral JAK1/JAK2/ACVR1 inhibitor, momelotinib, for the treatment of myelofibrosis with anemia, with an FDA decision expected by 16 June. GSK obtained the investigational therapy to bolster its late-stage cancer pipeline through its $1.9bn acquisition of *Sierra Oncology, Inc.* in April last year. (Also see "*Another New Home For Momelotinib As GSK Buys Sierra*" - Scrip, 13 Apr, 2022.)

Myelofibrosis is a rare form of blood cancer that occurs when the bone marrow produces abnormal blood cells, and can lead to anemia, fatigue and an enlarged spleen.

Momelotinib is designed to reduce spleen size, improve anemia and alleviate other symptoms. Evidence suggests that JAK1/2 inhibition is responsible for improving splenomegaly, while AVCR1 inhibition reduces circulating hepcidin, a hormone that is often elevated in myelofibrosis and contributes to anemia.

The US filing was based on the results from key Phase III trials, including the pivotal

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MOMENTUM trial, which met all its primary and key secondary endpoints. Furthermore, in the Phase III Simplify 1 trial, momelotinib demonstrated a significant reduction in spleen size, improvement in anemia, and a better safety profile compared to the current standard of care, Incyte's JAK1/2 inhibitor Jakafi (ruxolitinib).

"This suggests that momelotinib may offer a better treatment option for the disease. Regarding other treatment options, fedratinib, a JAK2/FLT3 inhibitor, is US FDA approved but, as with ruxolitinib, is hindered by exacerbating anemia. Consequently, there is an unmet need for agents that can ameliorate anemia in myelofibrosis, wherein GSK hopes momelotinib will have its success," said the Biomedtracker analysts.

However, they also pointed out that there are some potential roadblocks to the approval of momelotinib. One concern is the potential for long-term side effects, as JAK inhibitors have been associated with an increased risk of infections and other serious adverse events.

Intercept Pharmaceuticals' Obeticholic Acid For NASH

Potentially the first approved treatment for patients with precirrhotic liver fibrosis due non-alcoholic steatohepatitis (NASH) could come in the form of *Intercept Pharmaceuticals, Inc.*'s obeticholic acid (OCA). Intercept has been marketing OCA under the brand name Ocaliva for primary biliary cholangitis since 2016 and reported full-year US sales of nearly $286m for the product.

The application has a 22 June action date and the company believes its marketing of OCA in primary biliary cholangitis will give it a head start on reaching the right clinicians in NASH.

OCA is a derivative of natural human bile acid CDCA (chenodeoxycholic acid) and was granted a breakthrough designation for use in NASH by the US FDA in January 2015.

This is another application that has previously been subject to regulatory delays. On 23 December, Intercept refiled its NDA seeking approval of OCA, a FXR agonist, in pre-cirrhotic NASH patients, after a roughly 30-month process of responding to a June 2020 FDA complete response letter. (Also see "*Intercept Gifts Shareholders With NASH Refiling*" - Scrip, 23 Dec, 2022.)

The NDA resubmission included more robust data from the pivotal Phase III REGENERATE study showing that treatment with obeticholic acid 25mg demonstrated a significantly greater increase in the proportion of recipients achieving an improvement in liver fibrosis by at least 1 stage without worsening of NASH versus placebo; this improvement was more pronounced in individuals with more advanced disease at baseline.

However, the Biomedtracker analysts noted that in another Phase III study, REVERSE, the primary endpoint of ⩾ 1-stage histological improvements in fibrosis with no worsening of NASH

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in compensated cirrhosis patients after up to 18 months of therapy was not met. This will limit the size of the potentially eligible patient population.

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