NEWS IN BRIEF

Amylyx's ALS therapy secures FDA approval, as regulatory flexibility trumps underwhelming data

The FDA granted full approval to Amylyx's AMX0035 for the treatment of amyotrophic lateral sclerosis (ALS), a severe neurological disorder that causes paralysis and death. The agency convened its independent experts twice to discuss the therapy's mixed and complex data package. AMX0035 is the third drug to secure FDA approval for ALS, following now-generic riluzole in 1995 and Mitsubishi Tanabe's edaravone in 2017.

ALS is a rare disease that attacks and kills the nerve cells that control voluntary muscles. AMX0035 is a fixed-dose combination of two generic compounds — sodium phenylbutyrate and taurursodiol — intended to reduce neuronal cell death. The therapy's mechanism of action is unknown, but Amylyx hypothesizes that the drugs mitigate endoplasmic reticulum (ER) stress and mitochondrial dysfunction.

The FDA approved the treatment on the basis of results from a single phase II trial involving 137 patients with ALS, randomized 2:1 to treatment or placebo. Investigators monitored patients' rate of decline using the 48-point Amyotrophic Lateral Sclerosis Functional Rating Scale-revised (ALSFRS-R) score, over the course of 24 weeks. The mean rate of change in the ALSFRS-R score was −1.24 points per month on treatment and −1.66 points per month on placebo, as reported in the *NEJM*. Secondary outcomes did not differ significantly between treatment and placebo. A linked Editorial called the benefit "incremental", and noted the need for larger and longer trials to confirm the effect.

Adverse events on treatment were mainly gastrointestinal, and 19% of participants discontinued due to side effects.

The FDA gathered its independent advisors twice to discuss data from this trial. In March 2022, panellists voted 6 to 4 against approval. FDA reviewers and independent experts questioned the trial's small size, missing data, the drug's modest effect size, the statistical analyses and more. Amylyx submitted additional data, and a reconvened panel voted in September 7 to 2 in favour of approval.

Billy Dunn, the director of the FDA Office of Neuroscience, asked Amylyx during the second meeting to pledge to withdraw the drug if an ongoing 600-patient phase III trial fails. Results are due in 2024. "If the Phoenix trial is not successful, we will do what's right for patients, which includes taking the drug voluntarily off the market," said company co-CEO Justin Klee.

Amylyx will charge US$158,000 per year for the drug. The Institute for Clinical and Economic Review (ICER) estimates that a $9,100–$30,700 price tag would better reflect the drug's cost-effectiveness benefit. Edaravone costs around $170,000 per year — 50-times higher than ICER's suggested $1,400–$3,200 price tag.

The ALS field is set to stay in the drug development spotlight. In July, Biogen and partner Ionis filed for FDA approval of tofersen, despite a phase III failure for this SOD1-targeted antisense oligonucleotide. Investigators published the results of this trial in *NEJM* in September. In October, Clene said that its gold nanocrystal suspension CNM-Au8 missed the primary and several secondary endpoints of the phase II HEALEY ALS Platform Trial, but argued that a prespecified exploratory survival signal merits further study.

Asher Mullard

FDA approves first anti-IL-36 receptor antibody for rare skin disease

The FDA approved Boehringer Ingelheim's first-in-class anti-interleukin (IL)-36 receptor antibody, spesolimab, for flare-ups of a rare neutrophilic skin disease called generalized pustular psoriasis (GPP). This is the first treatment to secure FDA approval for GPP.

The potentially life-threatening disease is characterized by eruption of painful pustules that can be accompanied by fever, extreme fatigue and muscle weakness. Flare-ups have been managed in the USA with cyclosporine, retinoids, methotrexate and other off-label agents. Loss-of-function mutations in the IL-36 receptor antagonist gene are associated with GPP, and IL-36 levels are elevated in GPP skin — prompting hopes for a targeted antibody approach.

The FDA approved spesolimab on the basis of a phase II trial that randomized 53 patients with GPP to a single dose of treatment or placebo. The primary endpoint was a lack of visible pustules — assessed on the Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) pustulation subscore — at the end of week 1. In total, 54% of spesolimab recipients achieved this endpoint versus 6% of placebo recipients, the investigators reported in *NEJM* last year.

On day 8 of the trial, patients from both arms were eligible for a single dose of treatment — a crossover design that precluded longer-term comparison of spesolimab and placebo. "The episodic nature and variable severity of GPP flares present challenges in designing trials for patients with this disease," the investigators wrote in *NEJM*.

The most common adverse reactions were asthenia and fatigue, nausea and vomiting, headache, pruritus and prurigo, infusion site hematoma and bruising, and urinary tract infection. Infections were reported in 17% of treatment recipients in the first week, and in 47% of patients by week 12.

Boehringer is testing spesolimab in ongoing trials in other inflammatory indications, including ulcerative colitis, atopic dermatitis and hidradenitis suppurativa.

AnaptysBio is testing a potential class competitor called imsidolimab in a phase III GPP trial. Earlier this year, AnaptysBio discontinued development of this antibody in hidradenitis suppurativa due to lack of efficacy in phase II. Huabo Biopharm is also testing an anti-IL-36 receptor antibody.

Asher Mullard

FDA advisory committee votes for approval of first microbiome-based drug, despite data problems

Rebiotix's microbiota-based RBX2660 could secure FDA approval to reduce *C. difficile* infection (CDI) recurrence, following a positive vote from the agency's advisory committee. The FDA is due to rule on the live biotherapeutic — made from human stool — by mid-November, positioning it to potentially become the first microbiome-based drug to get the regulatory nod in the USA.

Each year in the USA, *C. difficile* infection causes around half a million illnesses — from mild diarrhoea to significant colitis — and 15,000–30,000 deaths. An estimated 10–30% of patients develop recurrent CDI after a first infection, and the risk for subsequent illness rises with each recurrence. Although antibiotics are used to treat recurrences, various infectious disease and gastroenterology practice guidelines recommend instead faecal microbiota transplant (FMT) — using microbes from a healthy gut to help keep the infection at bay. FMT products have not yet been approved by the FDA, however, and their formulation, strength and administration vary from application to application.

Companies including Ferring-subsidiary Rebiotix are working on standardizing the