Recent FDA Approvals Target *Zaire ebolavirus*

While the ongoing COVID-19 global pandemic continues to dominate both news cycles and the priority lists of pharmaceutical companies large and small, other viral diseases persist, sometimes catching the world off guard with devastating outbreaks that ravage communities in impoverished countries. The Ebola virus disease (EVD) is one.

Two drugs recently approved by the US Food and Drug Administration (FDA) treat disease caused by the *Zaire ebolavirus*, one of the three viral species responsible for the largest EVD outbreaks; *Bundibugyo ebolavirus* and *Sudan ebolavirus* are the other two species, but *Zaire ebolavirus* is the most fatal, according to the US Centers for Disease Control and Prevention (CDC). *Zaire ebolavirus* was linked to the largest EVD outbreak to date, in West Africa in 2014–2016. It infected more than 28,600 people and killed 11,310, most of them in Guinea, Sierra Leone and Liberia. An ongoing outbreak in the Democratic Republic of Congo is also associated with *Zaire ebolavirus*.

The recently approved medications share the same indication: for the treatment of *Zaire ebolavirus* infection in adults and children, including neonates born to mothers who had a positive reverse transcriptase-polymerase chain reaction (RT-PCR) for *Zaire ebolavirus*.

- Inmazeb (atoltivimab; maftivimab; odesivimab-ebgn), by Regeneron Pharmaceuticals Inc, is a fixed-dose combination of three glycoprotein-directed human monoclonal antibodies (mAbs). It received FDA approval on October 14, 2020.
- Ebanga (ansuvimab-zykl), a glycoprotein-directed human mAb, was developed by Ridgeback Biotherapeutics LP under licence from the National Institute of Allergy and Infectious Diseases (NIAID). It received FDA approval on December 21, 2020.

EVD incubation ranges from two to 21 days, according to the World Health Organization (WHO), but symptoms can develop suddenly. Initially, symptoms can include fever, fatigue, muscle, pain, headache and sore throat, the WHO says; subsequent symptoms can be very severe, including vomiting, diarrhoea, rash, impaired kidney and liver function, and internal and external bleeding. EVD is often fatal.

Initial *ebolavirus* infection in humans likely occurs via contact with wild animals, such as fruit bats or non-human primates, according to the CDC. The virus then spreads quickly from person to person, through direct contact with infected blood or bodily fluids, or via objects contaminated by infected blood or bodily fluids. Even after a person has recovered from EVD, certain bodily fluids can remain infectious, including semen.

Ebanga and Inmazeb Approvals Supported by the PALM Trial

Data from the PALM trial (NCT03719586) formed the basis for both approvals. The open-label, randomised controlled Phase II/III trial evaluated four investigational drugs: Inmazeb, Ebanga, remdesivir, and the control, ZMapp (porgaviximab; larcaviximab; cosfroviximab).[1] The primary endpoint was death at 28 days. PALM took place in the Democratic Republic of Congo, whose Ebola outbreak began in August 2018.

PALM opened in November 2018. The trial ultimately enrolled 681 subjects, including neonates and pregnant women. To qualify, patients had a positive RT-PCR for the nucleoprotein gene of *Zaire ebolavirus* and had not received other investigational treatments (excepting experimental vaccines) during the previous 30 days. In August 2019, the PALM data safety and monitoring board recommended that patients be assigned only to the Inmazeb and Ebanga arms, after an interim analysis pointed to the superiority of those drugs over ZMapp and remdesivir.

According to the FDA-approved product labels for Ebanga and Inmazeb:

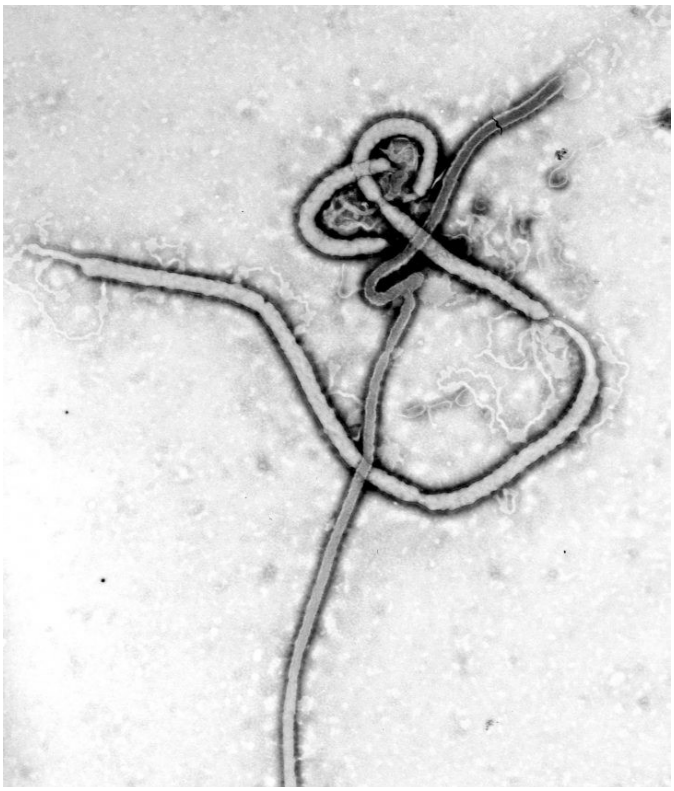
- 174 subjects received Ebanga (ansuvimab-zykl 50 mg/kg) as a single intravenous (IV) infusion. At 28 days, 35% (61) of Ebanga patients had died versus 49% (83) of patients in the control arm (p-value = 0.008).
- 154 subjects received Inmazeb (atoltivimab 50 mg/kg; maftivimab 50 mg/kg; odesivimab 50 mg/kg) IV as a single infusion. At 28 days, 34% (52) of Inmazeb patients had died versus 51% (78) of patients in the control arm (p-value = 0.0024).[2]

Both the Inmazeb and the Ebanga sponsors received a Material Threat Medical Countermeasure (MCM) Priority Review Voucher from the FDA, which can secure priority review for a future drug application. Section 565A of the Federal Food, Drug, and Cosmetic (FD&C) Act established the priority review voucher programme for material threat MCMs, defined as "medical products intended to diagnose, prevent, or treat diseases or conditions associated with chemical, biological, radiological, and nuclear (CBRN) threats and emerging infectious diseases," as the FDA's *Material Threat Medical Countermeasure Priority Review Vouchers* guidance document explains.

Vaccines Approved to Prevent Zaire ebolavirus Infections

The Inmazeb and Ebanga approvals followed the FDA's approval of the first vaccine to prevent *Zaire ebolavirus*: Ervebo, by Merck Sharp & Dohme Corp (Merck), on December 19, 2019. The European Medicines Agency (EMA) had approved Ervebo a few weeks earlier, on November 11, 2019. Both agencies authorised the vaccine's use in adults aged 18 years and older. Multiple other countries have since licensed Ervebo, including Burundi, Central African Republic, the Democratic Republic of the Congo, Ghana, Guinea, Rwanda, Uganda, and Zambia, according to the WHO.

Ervebo remains the only FDA-approved vaccine for any species of *ebolavirus*. The EMA also approved the Zabdeno vaccine, by Janssen Pharmaceutica NV, on July 1, 2020, authorising its use to prevent



Zaire ebolavirus infection in adults and in children aged one year and older.

The FDA's review of Ervebo safety and effectiveness took less than six months, a reflection of the "public health importance" of a vaccine to prevent Ebola virus disease, according to the agency. Approval came with a Tropical Disease Priority Review Voucher for Merck.[3] Like the FDA's priority review voucher programme for material threat MCMs, the tropical disease programme is intended to encourage sponsors to develop treatments in less-lucrative disease areas. Ebola rarely occurs in the US, the FDA has acknowledged; when US cases have arisen, they have involved healthcare workers who had treated EVD patients or people who were infected in other countries and then travelled to the US.

REFERENCES

1. Mulangu S, Dodd LE, Davey RT Jr, et al. A randomized, controlled trial of Ebola virus disease therapeutics. N Engl J Med. 2019 Dec 12;381(24):2293-2303.
2. The Inmazeb arm was added later in the trial, so PALM compared Inmazeb patients to patients in the control arm who were enrolled at the same time during the trial.
3. The FDA's *Tropical Disease Priority Review Vouchers* industry guidance, from October 2016, outlines requirements.

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