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Dynavax Hep B Vaccine Gets Second Panel Review; Scrutiny On Safety, Superiority

by Brenda Sandburg

After clinical hold, lost partnership and rejection by an advisory committee four years ago, Dynavax will again make its case for approval of Heplisav-B.

Dynavax Technologies Corp. is hoping that new safety and efficacy data for its hepatitis B vaccine *Heplisav-B* will win over FDA's Vaccines and Related Biological Products Advisory Committee, which voted against the product's approval in 2012.

The committee will review the vaccine candidate for immunization against hepatitis B virus infection in adults ages 18 years and older at its Nov. 16 meeting. The last time around the panel concluded that the available data did not support the safety of the vaccine. Dynavax then had planned a post-market 30,000 patient cohort study to compare Heplisav-B's safety to that of *GlaxoSmithKline PLC*'s *Engerix-B* but that did not assuage the panel's concerns. (Also see "*FDA Panel Considers Dynavax's Heplisav Safety Database Insufficient*" - Pink Sheet, 15 Nov, 2012.)

Members were worried about the vaccine's novel adjuvant, 1018, and the potential for it to cause an autoimmune response. A single case of Wegener's granulomatosis, a rare inflammation of blood vessels, resulted in an 18-month clinical hold on the vaccine's development in 2008. Soon after FDA placed the clinical hold Dynavax's partner *Merck & Co. Inc.* pulled out of their co-development deal and returned all rights to the vaccine to Dynavax.

When FDA lifted the clinical hold it allowed Dynavax to proceed with Phase III studies that targeted adults who were less responsive to current vaccine, including those over 40 years of age and those with chronic kidney disease, HIV, or chronic liver disease. (Also see "*FDA Lifts Clinical Hold On Dynavax's Hep B Vaccine Heplisav, Narrows Population*" - Pink Sheet, 10 Sep, 2009.).

The company faced another setback in February 2013 when the agency issued a "complete response" letter seeking more safety data in the broad population of adults and citing concerns

about the vaccine's adjuvant. After receiving the letter the company considered seeking approval for more restricted use, including in patients with chronic kidney disease and those 40 years and older. But Dynavax dropped the idea and announced later that year that it would instead collect additional safety data for approval in adults 18 to 70 years old. (Also see "*Dynavax Will Not Pursue Narrow Indication For Heplisav After Meeting With FDA*" - Pink Sheet, 10 Jun, 2013.)

Dynavax Wants Superiority Labeling Claim

Heplisav-B combines recombinant hepatitis B surface antigen with 1018, a synthetic cytosine phosphoguanine oligodeoxynucleotide that boosts immune response to the antigen. It is intended to be more potent and given in fewer doses than other hepatitis B vaccines. In clinical studies it was administered in two doses over one month, while GSK's non-adjuvanted Engerix-B is given in three doses.

Dynavax resubmitted its biologics license application in March and FDA subsequently requested individual trial data sets that had been provided as integrated data in the resubmission. The agency also extended the user fee action date by three months to Dec. 15.

More than 10,000 adults have received Heplisav-B throughout 11 clinical trials, including three pivotal Phase III trials comparing the vaccine to Engerix-B.

In January the company released positive top-line data from the pivotal Phase III HBV-23 safety and immunogenicity study of 8,368 patients who were randomized 2:1 to Heplisav or Engerix. The vaccine met two co-primary endpoints related to safety and immunogenicity.

Heplisav was noninferior to Engerix on the seroprotection rate at week 28, the main immunogenicity measure, and also demonstrated a statistically significant higher rate of seroprotection than Engerix-B in diabetics, a secondary immunogenicity measure. Dynavax expects superiority language for efficacy in labeling as well as a diabetes claim. (Also see "*Will Dynavax' HBV Vaccine Resubmission Make The Safety Grade?*" - Pink Sheet, 7 Jan, 2016.)

Adverse event rates were similar between the two treatment arms: 46% for Heplisav-B versus 46.2% for Engerix-B. The serious adverse event rate was 6.2% for Heplisav-B and 5.3% for Engerix-B. No cases of Wegner's granulomatosis or Tolosa-Hunt syndrome were reported.

Safety Database Expanded

In a January conference call, Dynavax CEO Eddie Gray said that based on the company's consultations with FDA, it had designed HBV-23 to include more than 5,500 additional participants in the Heplisav-B safety database to provide a sufficiently sized database for FDA to make a determination about the product. (Also see "*Dynavax Ready To Shake Up Hep B Market*" - Scrip, 8 Jan, 2016.)

Dynavax announced preliminary results from the trial at the American Diabetes Association's annual meeting in June. The company noted that according to the Centers for Disease Control and Prevention, people aged 23 to 59 with diabetes are about twice as likely to develop acute hepatitis B as those without diabetes. CDC recommends that adults age 19 to 59 be vaccinated against hepatitis B soon after being diagnosed with diabetes.

Berkeley, Calif.-based Dynavax develops novel vaccines and therapeutics in infectious and inflammatory diseases and oncology. Heplisav-B is one of its two lead product candidates. The other, SD-101, is an investigational cancer immunotherapeutic in Phase I/II studies.

Last year, Dynavax entered a new collaboration with Merck for two clinical trials to evaluate the potential synergistic effect of combining SD-101, a toll-like receptor 9 (TLR9) agonist, with Merck's anti-PD-1 therapy *Keytruda* (pembrolizumab) and with Merck's investigational anti-interleukin-10 immunomodulator MK-1966.