U.S. FOOD & DRUG ADMINISTRATION

Vaccines and Related Biological Products Advisory Committee Meeting

Hepatitis B Vaccine (Recombinant), Adjuvanted (Heplisav-B): Summary of Immunogenicity

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July 28, 2017

Background

- 2012 VRBPAC voted 13:1 that data from Phase 3 studies, HBV-10 and -16 were sufficient to support effectiveness.
- March 2016 Complete Response (CR) included revised clinical study reports (CSRs) for HBV-10 and -16 to address Applicant-identified errors in the immunogenicity analyses.
- Revised primary immunogenicity analysis for HBV-10 and -16 will be presented and compared with the primary immunogenicity analysis in the original CSRs.
- HBV-23 designed and conducted to address VRBPAC's recommendations to acquire additional safety data for Heplisav-B.
  - HBV-23 immunogenicity data not needed to establish effectiveness
  - HBV-23 immunogenicity data not presented

Phase 3 Trial Study Design: Similar Study Designs for HBV-10 and -16

- Subject and observer-blind, randomized, active control
- Three injections given
  - Heplisav-B at Weeks 0 and 4, placebo at Week 24
  - Engerix-B at Weeks 0, 4, and 24
- Primary immunogenicity endpoint: Difference in SPRs
  - HBV-10: Engerix-B (Week 28, 4 weeks post-last dose); Heplisav-B (Week 12)
  - HBV-16: Engerix-B (Week 32, 8 weeks post-last dose); Heplisav-B (Week 12)
- Success criteria: Non-inferiority
  - Success criteria defined as a non-inferiority margin of 10% for the between group difference in SPRs
  - Non-inferiority established if lower 2-sided 95% CI limit around Heplisav-B SPR – Engerix-B SPR > –10%

Study Design and Subject Enrollment

HBV-10 (Adults18-55 years of age):

- Randomized 3:1 to Heplisav-B or Engerix-B
- 2415 subjects ≥ 18 years of age enrolled
  - n=1809 Heplisav-B
  - n=606 Engerix-B

HBV-16 (Adults 40-70 years of age):

- Randomized 4:1 to Heplisav-B or Engerix-B
- 2452 subjects enrolled
  - n=1969 Heplisav-B
  - n=483 Engerix-B

HBV-10 and -16: Immunogenicity Results

Study (with year of CSR)	**Heplisav-B SPR (%)** (n/N)	**Engerix-B SPR (%)** (n/N)	**Estimated Difference in SPR[a]** (95% CI)
HBV-10 (2012)	**95.0** (1479/1556)	**81.1** (432/533)	13.9 (10.6, 17.6)
HBV-10 **(2016)**	**95.0** (1436/1511)	**81.3** (423/521)	13.7 (10.4, 17.5)
HBV-16 (2012)	**90.0** (1011/1123)	**70.5** (253/359)	19.6 (14.7, 24.7)
HBV-16 **(2016)**	**90.1** (1010/1121)	**70.5** (244/353)	19.6 (14.7. 24.8)

CI = Confidence interval; CSR: Clinical Study Report; N = number of subjects with non-missing results in the analysis population in the treatment group, n = number of subjects with post-injection anti-HBsAg levels ≥ 10 mIU/mL

[a]Non-inferiority supported if the lower bound of the 2-sided 95% CI (SPR difference of Heplisav-B – Engerix-B) is > -.10 (-10%).

HBV-10 and -16: Immunogenicity Conclusions

- Heplisav-B met pre-specified non-inferiority criteria for immunogenicity, as compared to the licensed active comparator hepatitis B vaccine, Engerix-B, for the revised per protocol population.

- Conclusions regarding immunogenicity of Heplisav-B based on the revised per protocol population data were unchanged.

Immunogenicity Conclusions

- Immunogenicity of Heplisav-B was established in the two phase 3 studies, HBV-10 and -16.
- Study HBV-23 was not needed for demonstration of effectiveness of Heplisav-B.