



**FOOD AND DRUG ADMINISTRATION**  
**CENTER FOR BIOLOGICS EVALUATION AND RESEARCH**

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MEMORANDUM

**ORIGINAL BLA REVIEW**

**DATE:** August 14, 2012

**FROM:** Marian Major, Ph.D.

**SUBJECT:** STN# 125428  
Preclinical Toxicology Data (Section 4.2.2)  
Sponsor: Dynavax  
Product: Hepatitis B Vaccine, recombinant (HEPLISAV)

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Dynavax submitted a Biologics License Application (BLA 125428) for HEPLISAV [Hepatitis B Vaccine (Recombinant)] for immunization against hepatitis B virus in adults 18 through 70 years of age.

HEPLISAV is a sterile, liquid that is administered as an intramuscular injection. It is formulated as 6000 ug/mL 1018 ISS adjuvant and 40 ug/mL HBsAg drug substance. The finished vial contains 4200 ug of 1018 ISS and 28 ug of HBsAg formulated in 0.7 mL of 8 mM sodium phosphate, 154 mM sodium chloride, 0.01% w/w polysorbate 80, pH 7.0 buffer. An administered dose of 0.5 mL contains 3000 ug of 1018 ISS and 20 ug of HBsAg in the buffered solution as described above. HEPLISAV does not contain preservatives.

This review covers the preclinical toxicology reports submitted in Section 4.2.2 of the original BLA 125428. The studies were carried out in cynomologous monkeys and rats to study the clearance of 1018 ISS from plasma and toxicity following subcutaneous administration.

**COMMENTS and CONCLUSIONS**

The test article 1018 ISS is cleared from the plasma within 24 hours at the highest dose tested (12.5mg/kg) when delivered subcutaneously in monkeys. The latest time point studied in rats was 4 hours post dosing. The test article was detectable at 4 hours only in the highest dose group (12.5mg/kg) at 2.1% of the total dose. For comparison, the final product (HEPLISAV) contains 3000ug 1018 ISS in a 0.5mL volume. For an adult weighing 60kg this would be equivalent to 0.05mg/kg. During vaccination this is delivered intramuscularly although it is not expected that a different route of administration would significantly impact the rate of clearance of the adjuvant.

Modest or minor clinical effects were seen most of which were reflective of the immunostimulatory nature of the test article and most resolved within the 4 week follow up period.

**Determination of 1018 ISS Plasma Concentration and Toxicity Following Subcutaneous Injection in Cynomolgus Monkeys (Dynavax Study 00-157, (b) (4) Study 898-002) and Rats (Dynavax Study 00-158, (b) (4) Study 898-001)**

The adjuvant 1018 ISS was quantified in plasma samples following subcutaneous dosing. All samples were treated by (b) (4) and analyzed by (b) (4)

(b) (4) was used to isolate the 1018 ISS from the plasma proteins. Quantitation of the isolated 1018 ISS was performed by (b) (4) against an internal standard oligonucleotide.

The (b) (4) method allows for the detection of oligonucleotides with preextraction plasma concentrations greater than 5 ug/mL.

**Toxicity:**

These studies were conducted to evaluate the toxicity of 1018 ISS following 8 weeks of once weekly subcutaneous dosing, followed by a 4-week recovery period.

Animals were dosed weekly as follows:

Group 1 (5M/5F (Monkeys) 15M/15F (Rats)): PBS

Group 2 (3M/3F (Monkeys) 10M/10F (Rats)): 0.5mg/kg 1018 ISS, maximum theoretical plasma concentration 14.3 ug/mL

Group 3 (3M/3F (Monkeys) 10M/10F (Rats)): 2.5mg/kg 1018 ISS, maximum theoretical plasma concentration 71.4 ug/mL

Group 4 (5M/5F (Monkeys) 15M/15F (Rats)): 12.5mg/kg 1018 ISS, maximum theoretical plasma concentration 357.1 ug/mL

The maximum theoretical plasma 1018 ISS concentration was based on an assumption of 70mL blood per kg body weight, and 0.5mL plasma per 1 mL blood. All dosed 1018 ISS was assumed to be in the plasma.

Observations for mortality, clinical signs (including qualitative food consumption), and body weights were conducted during the course of the study. Ophthalmoscopic, physical, and electrocardiographic examinations were conducted pretest and prior to the terminal and recovery necropsies. Various hematology and clinical chemistry evaluations were conducted pretest and at the end of the treatment and recovery periods.

No animals died during the course of this study, and no treatment-related effects on clinical findings, body weights, food consumption, ophthalmoscopic, physical, or electrocardiographic examinations, or clinical chemistry or urinalysis values were observed.

Clinical chemistry changes were observed in rats that indicated effects on the liver. A number of minor or modest changes were observed with most being class-effects of phosphorothioate oligonucleotides that have been well characterized in monkeys or reflective of the immunostimulatory properties of the test article. By the end of the 4 week recovery period most clinical and anatomic changes were diminished or reversed.

### **Plasma Concentration Studies in Monkeys**

The description of these studies was unclear. In the study reports it was stated that animals were dosed at Day 1 and Week 8. However, in the full study descriptions it was stated that samples were taken from animals used in the toxicology study and in this case animals were dosed weekly for 8 weeks. It appears the animals were dosed weekly, not at Day 1 and week 8, which would result in a higher exposure to the test article although testing was only performed on samples from Day 1 and Week 8.

For monkeys, blood samples were taken from each animal predose, and at 2, 6 and 24 hours post dose. For rats, 3 cohorts of 3 animals/sex/group were bled at each time point. Blood samples were taken at predose and at 1 and 4 hours post dose on Day 1 and week 8. The plasma was separated and stored frozen until analysis.

#### **Post Dose 1, Day 1:**

##### Monkey Study:

At 2 hours post dosing 1018 ISS was quantifiable in Groups 3 and 4, at 1.0% and 7.8% of the total dose, respectively.

At 6 hours post dosing the 1018 ISS was detected only in Group 4 at 0.85% of the total dose.

By 24 hours post dosing 1018 ISS was undetectable in all groups.

##### Rat Study:

At 1 hour post dosing 1018 ISS was quantifiable in Groups 3 and 4, at 2.4% and 49% of the total dose, respectively.

At 4 hours post dosing the 1018 ISS was detected only in Group 4 at 0.23% of the total dose.

#### **Post Week 8 Dose:**

##### Monkey Study:

At 2 hours and 4 hours post dosing 1018 ISS was detected only in Group 4, at 7.0% and 2.1% , respectively.

By 24 hours post dosing 1018 ISS was undetectable in all groups.

##### Rat Study:

At 1 hour post dosing 1018 ISS was quantifiable in Groups 3 and 4, at 24% and 53% of the total dose, respectively.

At 4 hours post dosing the 1018 ISS was detected only in Group 4 at 0.0.1% of the total dose.