

Mid-Cycle Meeting Summary

Application type and number: BL 125428/0
Product name: Hepatitis B Vaccine (Recombinant), Adjuvanted;
 (HEPLISAV-B)
Proposed Indication: For immunization against infection caused by all known subtypes of hepatitis B virus in adults 18 years of age and older
 [In the original BLA the indication was stated as “adults 18-70 years of age”]
Applicant: Dynavax Technologies Corporation
Meeting date & time: July 28, 2016
Committee Chair: Marian Major, PhD
RPM: Katherine Berkhousen, CAPT, USPHS
 Richard Daemer, PhD

Attendees:

Discipline	Name	Attended meeting?
Regulatory Project Manager (RPM)	Katherine Berkhousen Lead RPM	Y
	Richard Daemer, PhD Co-RPM	Y
Chair	Marian Major, PhD	Y
Clinical Reviewer	Darcie Everett, MD, MPH (safety)	Y
	Alexandra Worobec, MD (immunogenicity)	Y
CMC Reviewer	Iryna Zubkova, PhD	Y
	Brenda Baldwin, PhD (adjuvant)	Y
Animal Pharmacology Reviewer	N/A	
Clinical Pharmacology Reviewer	N/A	
Toxicology Reviewer	Andrew O’Carroll, DVM	Y
Developmental Toxicology Reviewer	N/A	
OCBQ/DMPQ Reviewer	Priscilla Pastrana	Y
OCBQ/DMPQ Consult Reviewer	Ellen Huang	Y
OCBQ/DMPQ/PRB Reviewer	Cheryl Hulme	N
Statistical Reviewer of clinical data	Mridul Chowdhury, PhD	Y
Statistical Reviewer of non-clinical data	Lei Huang, PhD	Y
Postmarketing Safety Epidemiological Reviewer	Maria Said, MD, MHS	Y
OCBQ/APLB Reviewer	Sonny Saini, Pharm.D.	Y
OCBQ/BIMO Reviewer	Bhanumathi Kannan	Y
OCBQ/DBSQC or OVRRLIB Reviewer	Karen Campbell	Y
	Hyesuk Kong, PhD	Y
	Lokesh Bhattacharyya, PhD	Y
	Muhammad Shahabuddin, PhD	N
	Anil Choudhary, PhD	Y
	Varsha Garnepudi, PhD	Y

Discipline	Name	Attended meeting?
Consult Reviewer(s)	N/A	
OCBQ/DMPQ/Inspectors	Priscilla Pastrana Ellen Huang	Y Y
CMC Inspector	Marian Major, PhD	Y
Labeling Reviewer-Carton/Container	Daphne Stewart	N
Other Attendee(s) who attended the meeting: OVRP, Director OVRP, Associate Director OVRP, IOD OVRP, IOD OVRP/DVRPA Director OVRP/DVRPA OVRP/DVRPA Branch Chief OVRP/DVRPA Branch Chief OVRP/DVRPA Branch Chief OVRP/DVRPA Team Lead OVRP/DVRPA Team Lead OVRP/DVRPA OVRP/DVRPA OVRP/DVP OBE/DB OBE/DB OBE/DE OCBQ/DMPQ OCBQ/DMPQ DBSQC	Marion Gruber, PhD Karen Farizo, MD Maureen Hess Valerie Marshall, LCDR Wellington Sun, MD Douglas Pratt, MD Elizabeth Sutkowski, PhD Rakesh Pandey, PhD Andrea Hulse, MD Meghan Ferris, MD, MPH Tim Nelle, PhD Julianne Clifford, PhD Rebecca Reindel, MD Sara Gagnetten, PhD Amelia (Dale) Horne, PhD Tsai-Lien Lin, PhD Deepa Arya, MD John (Jay) Elterman Pankaj (Pete) Amin William McCormick, PhD	

Background:

- HEPLISAV is a recombinant hepatitis B vaccine for active immunization against hepatitis B virus infection. This is the first BLA for Dynavax Technologies Corp. and the first time 1018 adjuvant is used in a vaccine.

- Data from two pivotal Phase 3 trials (HBV-16 and -10) including 4,864 randomized subjects (HEPLISAV: N=3,777, active comparator ENGERIX-B: N=1,087), ages 18 – 70 years, were submitted in the BLA. The BLA also contains data from eight supportive trials.
- The sponsor was asked to remove the superiority claims in their label.
- The initial prelicensure facility inspection (PLI) was done August 16 – 23, 2012, for the drug substance. A 13-point 483 was issued.
- PeRC held on October 3, 2012. A full PREA waiver was granted for birth through age 17 years.
- A VRBPAC meeting was held November 15, 2012, in which a majority of the committee Members voted that the safety database was too small to consider licensure at that time, as the vaccine contains a novel adjuvant. VRBPAC recommended a larger safety database.
- A CR Letter was issued on February 22, 2013.
- A Type C Meeting was held May 8, 2013 to discuss the path forward and design of the additional required pre-licensure safety study
- Dynavax submitted a complete CR on March 16, 2016, which included data from the additional pivotal safety study HBV-23 (N= 8,374 subjects), along with immunogenicity data for the subgroup with type 2 diabetes mellitus, and revised clinical study reports for pivotal phase 3 studies HBV-16 and -10.
- A Major Amendment letter was issued on April 18, 2016, due to a substantial amount of clinical data not previously reviewed or submitted to the application.
- A new PLI was performed on June 8-16, 2016. Five observations were issued in a Form FDA 483. Dynavax responded to these observations July 2016.

Report and Discussion:

1. Reviewer Reports.

Reviewer	Role	Final Report TBC	Notes
Marian Major, PhD	Chair		Roll call and Introduction Opening Remarks Decisions needed from Management: <ol style="list-style-type: none"> 1) VRBPAC decision 2) Confirm that HBV-23 immunogenicity data will not be reviewed. How and when would this decision be conveyed to the sponsor?
Alexandra Worobec, MD	Clinical- <i>immunogenicity</i> <i>See Appendix 1 for the</i>		<ul style="list-style-type: none"> • Issues noted that require further discussion relate to: The overall conduct of the previously submitted pivotal Phase 3 studies • Inconsistent subject disposition

<p>Darcie Everett, MD</p>	<p><i>immunogenicity briefing</i></p> <p>Clinical- <i>safety</i></p> <p><i>See Appendix 2 for the safety briefing</i></p>		<p>numbers based on the different, revised datasets and tabular summaries for newly included and excluded subjects in the per protocol populations submitted by the sponsor in multiple amendments from April - July 2016 , and</p> <ul style="list-style-type: none"> • Confirmation by statistics that the revised immunogenicity data for the primary immunogenicity endpoints in studies 10 and 16 (with the revised PP populations) using the SAS dataset are consistent with the primary immunogenicity endpoint data provided by the sponsor in the CSR for each respective study. <hr/> <p>Major safety findings of HBV-23:</p> <ul style="list-style-type: none"> • There was an imbalance in deaths and acute myocardial infarction, with more occurring in the HEPLISAV group. No imbalance was observed in the previous integrated summary of safety (ISS) from other clinical studies • Sixty-one subjects reported at least one potential new-onset AESI that was referred to the SEAC for evaluation, 39 subjects in HEPLISAV (0.70%) and 22 subjects in Engerix-B (0.79%). SEAC determined 4 to be new-onset confirmed autoimmune diseases and assessed none to be related. • One event of Takayasu arteritis in HEPLISAV was reported and assessed as most likely pre-existing by two FDA consultants. • One event of granulomatous dermatitis was reported in HEPLISAV group 70 days after second vaccination. Sarcoidosis was the leading differential diagnosis, but the diagnosis was never confirmed nor ruled out. • Bell's palsy was reported in 5 subjects in HEPLISAV (0.09%) and 1 subject in Engerix-B (0.04%). Two of the five Heparisav cases were associated with another concurrent cranial nerve palsy
---------------------------	---	--	---

			diagnosis.
Maria Said, MD, MHS	Pharmacovigilance	9/15/16	Review of the Pharmacovigilance Plan is under way. Further discussion within OBE is scheduled 7/25/16. Issues that need to be discussed include: (a) A potential postmarketing study (b) A pregnancy registry (c) Inclusion of the class effects of PS ODNs as potential risks in the Pharmacovigilance Plan
Mridul Chowdhury, PhD	Stats- clinical data	8/31/16	The applicant made several exclusions and inclusions in original subjects, in both pivotal studies: Protocols 10 and 16. IRs were made for SAS files of these changes. The SAS file for the new subjects contained subject IDs, but not immunogenicity information. So, the update of efficacy is possible only by match-merge of the excluded subjects with the original files. Fortunately, the updated results will be very close to the original results, because the exclusions (shown in next section) were not very many compared to the original sample sizes of N=1400, 2100 for Protocols 10 and 16 respectively. The analysis is ongoing.
Lei Huang, PhD	Stats -Bioassay		Bioassays were reviewed under IND and found to be acceptable. No issues.
Iryna Zubkova, PhD	CMC/Product		CMC review is completed, except outstanding IR (sent on 7/7/16). There are no significant changes in manufacturing process.
Brenda Baldwin, PhD	CMC/Adjuvant	8/31/16	Adjuvant review complete. Awaiting 7/7/16 IR response. Use of new assay to determine (b) (4) and product-related impurities of 1018. Proposing to replace the (b) (4) method with a (b) (4) [REDACTED]
	UNII code		Discuss if application should be made to name adjuvant through USAN – propose CpG 1018 (phosphorothioate

			oligonucleotide).
Andrew O'Carroll	Toxicology		The toxicology review was completed by a joint effort between S. Kunder and C. Wrzesinski in 2013 as part of the original submission. No new toxicology data submitted.
Karen Campbell/ Varsha Garnepudi	DBSQC	10/21/16	<p>Samples, standards and reagents have been requested and expected at the end of July.</p> <p>LRP template comments went out 7/26/16, with a 3 week turn around request.</p> <p>The testing plan draft has been written; this can be completed when:</p> <ul style="list-style-type: none"> • decisions about release tests can be made, • may be dependent on in-support testing, • post licensure testing has been determined <p>Major changes to the Product Insert are no longer expected. LRP template is acceptable.</p>
Anil Choudhary, PhD and Muhammad Shahabuddin, PhD	DBSQC	10/18/16	<p>The preliminary review of the IR response –CLR 26 to 41- suggests that Dynavax has addressed the issues for validation of test method for <i>in-vivo</i> potency, <i>in-vitro</i> (b) (4) and Identity, and (b) (4) of (b) (4) DP.</p> <p>For in-support testing of the launch lots, the reagents and samples have not yet been received.</p>
Lokesh Bhattacharyya, PhD	DBSQC	10/15/16	Preliminary review is ongoing for lot release tests and method validation. There are no obvious key findings to date. IR responses pending for (b) (4) assay and (b) (4) assay.
Hyesuk Kong, PhD	DBSQC (b) (4) Endotoxin	7/19/16	Review completed. No concerns.

Priscilla Pastrana and Ellen Huang	Facilities	10/31/16	<p>There are no potential issues in the review that we are aware of at this time that could prevent approval and impact the review timeline.</p> <p>The following review/documentation to be submitted to branch chief for review in October 2016:</p> <ul style="list-style-type: none"> • EIR in support to Dynavax GmbH Pre-License Inspection conducted on June 2016; • Review memo for Dynavax’s responses to the observations issued at the end of the Pre-License Inspection; • Review memo for the responses to the CR letter; • Review memo for the changes in the CMC/Facilities section of the re-submitted BLA.
Bhanu Kannan, MS	BIMO		<p>BIMO inspections are pending for all five clinical investigators (6 clinical sites total) for whom we issued inspection assignments for HBV-23.</p> <p>122 and 222 Radiant Research, Inc. Chicago, Illinois</p> <p>119 Clinical Research Advantage, Inc. Birmingham, Alabama</p> <p>124 Clinical Research Advantage, Inc Las Vegas, Nevada</p> <p>132 Radiant Research, Inc. Columbus, OH</p> <p>138 Radiant Research, Inc. Atlanta, GA</p>
Sonny Saini, PharmD Daphne Stewart	Labeling		<p>No issues thus far. Labeling discussions have not yet started.</p> <p>Minor issues to be resolved include coloring and NDC codes.</p>

2. For PDUFA V Program submissions:

N/A

3. If the application will be discussed at an Advisory Committee (AC), review potential issues for presentation.

The clinical team, supervisors and OVRP IOD discussed the need for VRBPAC. Discussion ensued regarding:

- **the clinical review is still ongoing,**
- **1st cycle review identified two subjects who developed rare autoimmune diseases, raising the concern about a potential signal of serious risk related to the use of HEPLISAV; the 2nd cycle clinical review has identified preliminary safety concerns that need more extensive review and analysis,**
- **the (Dynavax) revised datasets and tabular summaries of data submitted for study HBV-16 have not been reconciled and inconsistencies have been identified in the 3 ‘different’ datasets and/or tabular summaries that Dynavax has submitted for CBER review thus far,**
- **the VRBPAC decision date is today**

Based on these discussions it was determined that a VRBPAC would likely need to take place.

4. Determine whether Postmarketing Requirements (PMRs), Postmarketing Commitments (PMCs), or a Risk Evaluation Mitigation Strategy (REMS) are needed.

CBER Safety Workgroup has been notified of potential Title IX PMR and placed on schedule for Oct/early Nov for potential topics.

5. National Drug Code (NDC) assignments to product/packaging (excludes devices).

Partial NDC code was submitted—only the labeler code. The sponsor will need to provide the entire NDC for our review. Label review is underway.

6. Proper naming convention.

Proprietary: **HEPLISAV-B**

Non-proprietary: **Hepatitis B Vaccine (Recombinant), Adjuvanted**

7. Status of inspections (GMP, BiMo, GLP) including issues identified that could prevent approval and the establishment inspection report (EIR).

GMP PLI:

- **A new PLI of Dynavax GmbH in Düsseldorf, Germany, was conducted from June 8-16, 2016. Inspectors: Marian Major/Priscilla Pastrana/Ellen Huang.**
- **Five observations were issued in a Form FDA 483 to Dynavax at the end of the PLI. Firm’s responses to these observations were received on July 11, 2016.**
- **PLI of the following facilities in support for the manufacture and testing of HEPLISAV™ [Hepatitis B Vaccine, Recombinant (Adjuvanted)] or Drug Product were waived:**
 - **Rentschler Biotechnologie GmbH, Laupheim, Germany;**



GCP:

- **GCP inspections are pending. There are 5 principal investigators and 6 sites that will receive inspections (one of the PIs has 2 sites).**

Review

8. Major target and milestone dates from RMS/BLA. Discuss pending dates of targets and milestones (e.g. Late-Cycle meeting, Advisory Committee, labeling discussion).

Mid-point Meeting	July 28, 2016
PMC/PMR/SWG Determination:	Sep 11, 2016
Draft Reviews to Supervisor	Sep 15, 2016
PMC/PMR/SWG Notify applicant	Nov 15, 2016
Reviewers Final Reviews	October 15, 2016
Signed/Uploaded Due:	Nov 15, 2016
Final Review Addendum Due*:	Nov 15, 2016 (T-30)
Complete BIMO Inspections:	Oct 15, 2016 (T-60)
Press Release –contact M. Hess	Oct 31, 2016
Labeling Meetings:	TBD
Labeling Comments to Applicant:	Nov 15, 2016 (T-30)
Late-Cycle Briefing Package*:	N/A
Late-Cycle Meeting*:	N/A

9. Establish a labeling review plan and agree on future labeling meeting activities.

Dynavax will need to be notified to revise their PI by removing all superiority claims. This will make a better starting point to review the PI. Time point for this notification is to be determined.

10. Components Information Table was obtained and notification was sent to the Data Abstraction Team (DAT) if discrepancies were found per *SOPP 8401.5: Processing Animal, Biological, Chemical Component Information Submitted in Marketing Applications and Supplements*. If not complete, indicate date it will be completed.

John Bishop and Craig Lazar (and the CBER ABC email account) were notified in April 2016. Email communication between their office and the CMC reviewers and the review team has addressed their questions.

11. New facility information is included in the application, requiring implementation of regulatory job aid *JA 910.01: Facility Data Entry*.

This has been completed (in May 2016).

12. Status of decisions regarding lot release requirements, such as submitting samples and test protocols and the lot release testing plan.

This requires discussion between DBSQC and the CMC Product reviewers to determine which tests will be performed as release tests post licensing. This will be documented in the Testing Plan. We are waiting for samples to perform the in-support testing which may impact our decision on what tests will be performed post licensing.

13. Unique ingredient identifier (UNII) code process has been initiated. See regulatory job aid *JA 900.01: Unique Ingredient Identifier (UNII) Code* for additional information.

The submitted Heplisav-B SPL already contains UNII codes minus the adjuvant code. We are under active discussion with the UNII code team for their concurrence and for the adjuvant code.

14. PeRC presentation date is set, and the clinical reviewer has addressed waiver/deferral/assessment of the PREA decision.

N/A

PeRC Discussion: 10/3/2012

PREA- Full Waiver as the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients.

15. Additional Discussion Items:

- **The clinical reviewers presented a summary of the immunological and safety review to date. See Appendices 1 and 2.**
- **The Dynavax re-submission is a response to a CR and the clinical portion of the CR should have addressed only the safety concerns outlined in the CR letter, as immunogenicity data was previously reviewed in healthy adults 18-70 years of age in Studies DV2-HBV-10 and -16 and supported the non-inferiority of the immune response to HEPLISAV when compared with Engerix-B. However, Dynavax submitted revised immunogenicity data for studies HBV-10 and HBV-16, as well as additional unsolicited immunogenicity data from study HBV-23.**
- **The review team discussed that Dynavax submitted this new information to support an additional indication in the package insert and/or support claims of superiority in diabetics as well as other sub-populations who may have reduced responses to currently licensed hepatitis B vaccines. Previous teleconference discussions with Dynavax were referenced and reviewers recalled that CBER clearly discussed with the Dynavax team that CBER had not agreed that any of the diabetic immunogenicity data in Study HBV-23 would be presented in any section of the package insert. During that teleconference CBER stressed that generally we do not permit superiority claims in our labels and Dynavax agreed that they would *not* make a superiority claim**

and that what is included in the label would be a review issue. Furthermore, it was noted that DVRPA management had discussed the modified indication in diabetics with Carla Vincent and with Chris Joneckis (Office of the Director, Review Management), who both agreed that it was consistent with agency policy that the diabetic immunogenicity data should be submitted in a separate supplement because it is intended to support a new or modified claim. The review team received OVRRIOD concurrence to not review the immunogenicity data for study HBV-23.

16. Action Items:

- 1. Notify Dynavax of VRBPAC decision.**
- 2. Following confirmation from OVRRIOD that HBV-23 immunogenicity data will not be reviewed, determine how and when this decision will be conveyed to the sponsor.**
- 3. Request complete NDC code from Dynavax.**

Appendix 1

STN 125428 (Clinical Immunogenicity)

Application type and number: BLA STN 125428

Product Name: HEPLISAV, Hepatitis B Vaccine (Recombinant) with 1018 ISS Adjuvant

Proposed indication: Active immunization against all subtypes of hepatitis B virus infection in healthy adults 18-70 years of age

Applicant: Dynavax

Reviewer Name: Alexandra S. Worobec, M.D.

Discipline: Clinical Reviewer (Immunogenicity)

Clinical Immunogenicity Findings:

Studies submitted:

- Revised study DV2-HBV-10
- Revised study DV2-HBV-16: Noninferiority and lot consistency study
- Study DV2-HBV-23: not reviewed for immunogenicity (bundling of diabetic data not allowed)

Revised Study DV2-HBV-10 (a.k.a. Study 10)

Study Design:

- Phase 3, subject- and observer-blind, multi-center, randomized, controlled study (n ~ 2400).
- Per-Protocol (PP) Population definition:
 - Subjects who met the eligibility criteria
 - Did not violate the protocol in a substantial manner.
 - Received all protocol-specified study injections
 - Had anti-HBsAg measurements and all injections within the specified day ranges
 - Had an anti-HBsAg measurement at their primary endpoint

Revised Subject Disposition Results (Table 1):

- Exclusion of 58 additional subjects in the revised PP population based on the applicant's audit of data they submitted in the original BLA submission with respect to pre-existing subject exclusion criteria and protocol deviations.
- Most common cause reported for exclusion: pre-existing autoimmune disorder.
- Reasons for exclusions of these 58 subjects were appropriate.

- Total proportion of subjects excluded from the PP population small compared to the original PP population (2.8% for HEPLISAV and Engerix-B combined).

Table 1: Subject Accounting for the Revised Per-Protocol Population for Study DV2-HBV-10: Adults 18-55 years of age

	HEPLISAV (n)	Engerix- B (n)	Total (n)
Randomized Population	1809	606	2415
Original PP Population	1557	533	2090
Total Number of Subjects excluded from the Randomized Population (n, % of randomized population)	252 (13.9%)	73 (12%)	325 (13.5%)
Revised PP Population	1511	521	2032
Net number of subjects excluded in the PP Population in the Revised Analysis	46	12	58
Percentage of Subjects from the Original PP Population Excluded in the Revised PP Population	46/1557 (3.0%)	12/533 (2.3%)	58/2090 (2.8%)
Total Number of Subjects in the Revised PP Population excluded from the Randomized Population (n, % of randomized population)	298 (16.5%)	85 (14.0%)	383 (15.9%)
Total Number of Subjects Excluded from the Original PP Population	48	15	63
Exclusion due to Pre-existing Autoimmune Disease	44	14	58
Exclusion due to Incorrect Study Treatment for Dose 3	3	0	3
Exclusion Due to Pregnancy	1	1	2
Total Number of Subjects Incorrectly Excluded from the Original PP Population (Included in the Revised PP Population)	2	3	5
Inclusion due to Absence of Pre-existing Autoimmune Disease	1	3	4
Inclusion due to Absence of Pregnancy	1	0	1
Net Number of Subjects Excluded from the Original PP Population	46	12	58

Table compiled from: BLA STN 125428, Amendment 42, Section 16.2.3. Patients Excluded from the Efficacy Analysis, pages 1-97, BLA STN 125428, Sequence 47, Dynavax Partial Response to FDA Request for Information dated 27 May 2016, BLA STN 125428, Sequence 52, Dynavax Complete Response to FDA Request for Information Dated 12 July 2016

Revised Immunogenicity Analysis with the Revised PP Population:

- Primary immunogenicity endpoint defined as: the seroprotective rate (SPR) at Week 12 following two injections of HEPLISAV compared with the SPR at Week 28 following three injections of Engerix-B, using the PP population for adult subjects 18-55 years of age.
- The SPR difference with re-analysis changed from -13.91% to -13.74%. The upper bound of the 95% CI changed from -10.61% to -10.42% and met the primary endpoint of non-inferiority defined as the upper bound of the 95% CI being less than 10%.
- Data presented in Table 2.
- Still need to confirm whether the statistical reviewer can verify the primary immunogenicity endpoint data in the CSR by using the datasets.
- Applicant-initiated revisions to the PP population also had a negligible effect on secondary immunogenicity endpoints, with no change in the conclusions of the study (data not shown).

Table 2: Revised Primary Immunogenicity Endpoint Analysis (Study DV2-HBV-10): SPR for HEPLISAV (Week 12) compared with Engerix-B (Week 28) using the Per-Protocol Analysis Population, Adults 18-55 years of age

Visit	HEPLISAV ^a SPR (%) (n/N)	Engerix-B ^b SPR (%) (n/N)	Estimated Difference in SPR ^c (Engerix-B – HEPLISAV (95%) CI)	Non-inferiority Criteria Met? ^d (Yes/No)
Week 12/ Week 28	95.0 % (1436/1511)	81.2 % (423/521)	-13.7 (-17.5, -10.4)	Yes

CI = Confidence interval, 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 Study injections were given at Weeks 0, 4, 24 (placebo).

^b Study injections were given at Weeks 0, 4, 24.

^c Estimated response (proportion), their difference, and associated confidence intervals are based on a statistical analysis model adjusting for age groups (18-39 years vs. 40-55 years). The Miettinen and Nurminen method was used to calculate the 95% confidence intervals.

^d Non-inferiority is supported if the upper bound of the 2-sided 95% CI is < 0.10 (+10%).

Source: *BLA STN 125428, Clinical Study Report, HBV-DV2-10, Section 11.1.1, Table 11-1, page 63 of 204*

BLA STN 125428, Table 11-1, page 278 if 442, submitted 15 March 2016

Study 10 Conclusions:

- Small number of excluded subjects in the revised PP population relative to the original PP population (2.8% total).

- No significant impact of the revised PP population on the revised primary immunogenicity endpoint or primary immunogenicity endpoint conclusion.
- HEPLISAV shown to be noninferior to Engerix-B.
- Applicant-initiated revisions of PP population also had a negligible effect on secondary immunogenicity endpoints, with no change in the overall conclusions of this study.
- Still awaiting confirmation that the statistical reviewer can verify the primary immunogenicity endpoint findings reported in the CSR using the datasets.
- The need to exclude additional subjects from the original analysis based on improper study enrollment combined with post-hoc immunogenicity analysis raise concerns about the overall conduct of this study.

Revised Study DV2-HBV-16 (a.k.a. Study 16)

Study Design:

- Phase 3, observer-blinded, randomized, parallel-group, multi-center study comparing the safety and immunogenicity of HEPLISAV to Licensed Vaccine (Engerix-B) among Healthy Adults 40 to 70 years of Age (n~ 2000 subjects).
- *Two co-primary endpoints (See Table 3):
 - Seroprotective rate (SPR) after the final active injection
 - Lot consistency in three consecutively manufactured lots of HEPLISAV from the manufacturing process after minor modification, measured by GMC at 4 weeks after the last active dose of HEPLISAV (Week 8)
- For the primary objective of lot consistency, the allocation ratio was 1:1:1.
- Study also included a bridging lot analysis of an older lot (TDG006) of HEPLISAV with the three final lots (TDG008, 009, and 010)—a secondary endpoint.

Table 3: Definition of Co-primary Endpoints for Study 16

Study 16: Primary Endpoint	Definition	Criteria for Establishing Noninferiority
SPR after the final active Injection	Proportion of subjects with a seroprotective immune response (anti-HBs Ab level ≥ 10 mIU/mL)	HEPLISAV declared non-inferior to Engerix-B with respect to SPR if lower limit of the 95% CIs of the difference in SPRs (HEPLISAV seroprotection rate at Week 12 minus the Engerix-B seroprotection rate at Week 32) $> -10\%$

Lot Consistency for 3 consecutively manufactured lots of HEPLISAV	GMC at 4 weeks after last active dose of HEPLISAV (Week 8)	Lot consistency established if all three CIs for the pairwise ratios of GMCs embedded in the interval between 2/3 (0.667) and 1.5
---	--	---

Applicant-initiate

d Revised Subject Disposition Results (with source, as the clinical reviewer noted discrepancies between sources):

- A net of **8** additional subjects excluded from the original noninferiority PP population (CSR).
- A net of **26** additional subjects excluded from the original lot consistency study (CSR).
- The net number of subjects excluded for both revised PP populations derived from:
 - The total number of subjects excluded – total number of subjects now included (who were originally improperly excluded) in the original PP populations.
- Total proportion of subjects excluded from the PP population small compared to the original PP population (generally < 2.0% for the two PP populations)
- Reasons for exclusion (in decreasing order of frequency):
 - Administration of vaccine not properly stored
 - Did not meet enrollment criteria:
 - Pre-existing autoimmune disease
 - Anti-HBs > 5.0 mIU/uL at baseline
 - Did not receive correct vaccine as randomized
 - Prohibited medication taken
- Appropriate reasons for subject exclusion.
- Select subject disposition data, including accounting of the excluded PP population subjects presented in Table 4.
- Discrepancy in the numbers of subjects newly excluded and newly included in the revised PP populations found between the May and July IR responses submitted by the sponsor. Discrepancy found to due to inconsistent labeling of subjects' exclusion status in the submitted datasets.

Table 4: Revised Subject Accounting for Study DV2-HBV-16: Non-inferiority and Lot-to-Lot Consistency Per Protocol Populations (Adults 40-70 years of age)

Subject Disposition	Lot TDG008	Lot TDG009	Lot TDG010	HEPLISAV consistency Lots Total ^a	Lot TDG006	Engerix-B	Total
Randomized	481	483	477	1441	528	483	2452

Subject Disposition	Lot TDG008	Lot TDG009	Lot TDG010	HEPLIS AV consistency Lots Total^a	Lot TDG006	Enerix-B	Total
Total Number of Subjects in the PP Population excluded from the Randomized Population (n, % of randomized population)	53 (11.0%)	45 (9.3%)	53 (11.1%)	151 (10.5%)	73 (13.8%)	63 (13.0%)	438 (17.9%)
Original Noninferiority Per Protocol Population	366 (76.1%)	375 (77.6%)	382 (80.1%)	1123 (77.9%)	NA	359 (74.3%)	1482
Total Number of Subjects in the Original Noninferiority PP Population excluded from the Randomized Population (n, % of randomized population)	115 (23.9%)	108 (22.4%)	95 (19.7%)	318 (22.1%)	NA	124 (25.7%)	442 (23.0%)
Revised Noninferiority Per Protocol Population	366 (76.1%)	375 (77.6%)	380 (79.7%)	1121 (77.8%)	NA	353 (73.1%)	1474 (76.6%)
Net change in Noninferiority PP subjects in the Revised Analysis	0 (0%)	0 (0%)	2 (0.5%)	2 (0.2%)	NA	6 (1.7%)	8 (0.5%)
Total Number of Subjects in the Revised Noninferiority PP Population excluded from the Randomized Population (n, % of randomized population)	115 (23.9%)	108 (22.4%)	97 (20.3%)	320 (22.2%)	NA	130 (26.9%)	450 (23.4%)
Original Lot Consistency Per Protocol Population:	428 (89.0%)	438 (90.7%)	424 (88.9%)	1290 (89.5%)	455 (86.2%)	420 (87.0%)	2165 (88.3%)
Revised Lot Consistency Per Protocol Population	423 (87.9%)	427 (88.4%)	414 (86.8%)	1264 (87.7%)	NA	NA	NA

Subject Disposition	Lot TDG008	Lot TDG009	Lot TDG010	HEPLISAV consistency Lots Total ^a	Lot TDG006	Engerix-B	Total
Net change in PP subjects in the Revised Analysis	5 (1.2%)	11 (2.5%)	10 (2.4%)	26 (2.0%)	NA	NA	NA
Total Number of Subjects in the Revised Lot-to-Lot Consistency PP Population excluded from the Randomized Population (n, % of randomized population)	58 (12.1%)	56 (11.6%)	63 (13.2%)	177 (12.3%)	NA	NA	NA

N= number of subjects randomized to the treatment group; NA: Not applicable to PP Population.

^a Lots TDG008, TDG009, and TDG010.

Source: *BLA STN 125428, Amendment 42, Revised Clinical Study Report, DV2-HBV-16, Section 10.2 Disposition of Subjects, Pages 296-297 of 480*

Revised Immunogenicity Analysis with the Revised PP Population:

- Revised PP population data resulted in a no change in the conclusions regarding both primary immunogenicity endpoints per revised CSR.
- Negligible numeric change in the SPRs for HEPLISAV and Engerix-B and no change in the primary endpoint difference between SPRs of 19.6% or the lower bound of the 95% CI of the difference of 14.7%. The result met the primary endpoint of non-inferiority, which was defined in this trial as the lower bound of the 95% CI being greater than -10%.
- Revision in the lot consistency PP population resulted in minimal changes in the ratios of geometric mean concentrations (GMC) between lots and no change in the conclusions regarding lot-to-lot consistency.
- Data presented in Tables 5 and 6.
- Still need to confirm the primary immunogenicity endpoint data in the CSR for study 16 with SAS file data (need statistics input).

Table 5: Primary Immunogenicity Endpoint Analysis for Study DV2-HBV-16 with the Revised PP Analysis Population: SPR for HEPLISAV (Week 12) compared with Engerix-B (Week 32)

Visit	HEPLISAV ^a SPR (%) (n/N)	Engerix-B ^b SPR (%) (n/N)	Estimated Difference in SPR ^c (HEPLISAV-Engerix-B (95% CI)	Non-inferiority Criteria Met? ^d (Yes/No)
Week 12/ Week 32	90.0 % (1010/1121)	70.5 % (249/353)	19.6% (14.7%, 24.8%)	Yes

CI = Confidence interval, 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 Study injections were given at Weeks 0, 4, 24 (placebo).

^b Study injections were given at Weeks 0, 4, 24.

^c Two-sided 95% CIs of the difference in seroprotection rates between the HEPLISAV group at 12 weeks and the Engerix-B group at 32 weeks was supported using the Newcombe score method with continuity correction.

^d Non-inferiority was supported if the lower bound of the 2-sided 95% CI was $> -10\%$.

Source: *BLA STN 125428, Clinical Study Report, DV2-HBV-16, Table 11-1, Page 83 of 215, BLA STN 125428, Amendment 1, Clinical Study Report, DV2-HBV-16, Table 11-1, Page 322 of 480*

Table 6: Primary Immunogenicity Endpoint Analysis for Study DV2-HBV-16: Anti-HBsAg Geometric Mean Concentrations (mIU/mL) among HEPLISAV Consistency Lots at Week 8 and Week 12 (Revised Lot Consistency PP Population; Adults 40-70 years of age)

Visit	Lot TDG008 GMC (mIU/mL); 95% CI	Lot TDG009 GMC (mIU/mL); 95% CI	Lot TDG010 GMC (mIU/mL); 95% CI
Week 8 ^a	36.1 (28.1, 46.4) N=428	32.1 (24.8, 41.5) N=427	39.8 (30.7, 51.5) N=414
Week 12 ^b	80.3 (65.4, 98.5); N=420	81.2 (65.8, 100.2); N=424	89.0 (72.0, 109.9); N=412
	Adjusted GMC Ratio^a (95% CI) Lot TDG008/Lot TDG009	Adjusted GMC Ratio^a (95% CI) Lot TDG010/Lot TDG008	Adjusted GMC Ratio^a (95% CI) Lot TDG010/Lot TDG009
Week 8 ^a	1.1 (0.8, 1.5)	1.1 (0.8, 1.5)	1.2 (0.9, 1.7)
Week 12 ^b	1.0 (0.8, 1.3)	1.1 (0.9, 1.4)	1.1 (0.9, 1.4)

CI = Confidence interval, GMC = geometric mean concentration, N = number of subjects with non-missing results in the analysis population in the treatment group. GMCs were adjusted for lot, center and age category.

^a 4 weeks after the last dose of HEPLISAV.

^b 8 weeks after the last dose of HEPLISAV.

Source: *BLA STN 125428, Clinical Study Report, DV2-HBV-16, Table 11-2, Page 85 of 215, BLA STN 125428, Amendment 1, Clinical Study Report, DV2-HBV-16, Table 11-2, Page 322 of 480.*

Study 16 Conclusions:

- Number of excluded subjects in the revised PP population small relative to the original PP population (generally < 2.0% for both PP populations).
- No significant impact of the revised PP population on the revised primary immunogenicity endpoints.
- Minor numerical change in SPR and GMCs with no change in the study's conclusion regarding immunogenicity.
- HEPLISAV shown to be noninferior to Engerix-B.
- Lot-to-lot consistency demonstrated for the three consecutively manufactured lots of HEPLISAV.
- Still awaiting confirmation of primary immunogenicity endpoint findings reported in the CSR by the SAS dataset (statistics input needed).
- Accounting discrepancies for the excluded PP population subjects found between the datasets and tables or corresponding documents submitted in the two IR responses.
- The combination of the need to exclude additional subjects from the original analysis based on improper study enrollment combined with subject accounting discrepancies and post-hoc immunogenicity analysis raise concerns about the overall conduct of this study.

OVERALL CONCLUSIONS AND OUTSTANDING BUSINESS:

- No significant decrease in the revised PP populations for studies 10 and 16.
- No significant numerical change in the SPRs or GMCs used to determine the co-primary immunogenicity endpoints, no change in the noninferiority comparison between HEPLISAV and Engerix-B, and no change in the lot consistency determination.
- Still need to confirm with the statistical reviewer that the revised immunogenicity data in the CSR can be verified using the datasets.
- Still need to confirm which subjects were actually excluded from the revised noninferiority PP population for study 16, as the applicant has submitted conflicting information.
- Global concerns raised regarding overall conduct of the two pivotal studies (10 and 16):

- Need to exclude additional subjects from the original analysis based on improper study enrollment.
- Subject accounting discrepancies across different datasets submitted to support the revised CSR (.xpt dataset provided in CR response and the two subsequent IR responses).
- The subject accounting discrepancies seen in the two IR responses appear due to differences in the applicant's designation of subjects' PP population status (i.e., whether labeled as excluded or included in noninferiority or lot consistency PP population).
- Options for addressing the inconsistencies seen amongst the different subject disposition data sources should be discussed at the mid-cycle meeting, and include:
 - Additional IR request and/or direct discussion with the sponsor about the inconsistencies detected for accounting of the revised PP population.
 - CR with a discussion of the inconsistencies in subject accounting for the excluded PP population subjects in Study 16.
 - Consideration for not approving this product, based on concerns about the general quality of the pivotal clinical trials conducted and use of post-hoc data to support licensure (i.e. not performed according to standards of being "adequate and well controlled" to support licensure).

Appendix 2

Summary of Safety findings for HEPLISAV-23

- HBV-23 was a Phase 3, randomized, observer-blind, active-controlled (Engerix-B) study of the safety and immunogenicity of HEPLISAV in adults 18 to 70 years of age.
 - HEPLISAV two-dose series at Weeks 1 and 4; placebo given at Week 24.
 - Engerix-B was given as a three-dose series at Week 1, 4, and 24.
 - Conducted at 40 US sites.
 - Safety monitoring: Medically attended events (MAEs), serious adverse events (SAEs), adverse events of special interest (AESIs), and autoimmune adverse events (AIAEs) were monitored for one year following the second vaccination. A laboratory sub-study was performed at time points throughout the study to evaluate hematology, chemistries, urinalysis, and thrombotic parameters. Solicited adverse events were not monitored.
- Safety population of HBV-23 consisted of a total of 8,368 subjects who received either HEPLISAV (5,587) or Engerix-B (2,781) (randomized 2:1)
 - Total Safety Database: 10,038 subjects who received HEPLISAV (compared to 4,200 subjects who received Engerix-B).
- Study completion rate through Week 56 was 91.5% for both study groups combined.
- Demographics: 50.6% Male, Mean age 50.4 years (SD 11.7), 25.3% were 60 years or older, 71% were white, 26% black, 1% Asian, 1% other; 9% were Hispanic.
- Deaths (Table 1)
 - 0.45% HEPLISAV (25 subjects), 0.25% Engerix-B (7 subjects).
 - Excluding deaths clearly due to overdose or injury: 0.29% HEPLISAV (16 subjects), 0.14% Engerix-B (4 subjects)
 - Deaths within 1 month: HEPLISAV - 1 subject, Engerix-B - 2 subjects
 - Deaths within 3 months: HEPLISAV - 5 subjects, Engerix-B - 3 subjects
 - Prior studies: Two deaths in HBV-16, one 46 year-old HEPLISAV-recipient with no relevant past medical history died of Pulmonary embolus (b) (6) days after the second study injection. One Engerix-B recipient died following heart attack (b) (6) days after the second dose. Both determined to be unrelated by Investigator and the Clinical Reviewer of the original BLA.
 - ISS: 0.26% HEPLISAV (26 subjects), 0.19% Engerix-B (8 subjects); Excluding overdoses and injuries 0.17% HEPLISAV (17 subjects), 0.12% Engerix-B (5 subjects)

- SAEs
 - 6.2% HEPLISAV, 5.3% Engerix-B
- Cardiac events
 - Previous studies: No imbalance in acute myocardial infarction (AMI) in previous ISS. Any cardiac SAE was reported by 0.2% HEPLISAV recipients and 0.5-0.6% Engerix-B recipients in previous ISS.
 - AMI SAEs reported in 0.25% HEPLISAV (14 subjects), 0.04% Engerix-B (1 subject) recipients. Any cardiac SAE reported in 0.91% HEPLISAV (51 subjects), 0.54% Engerix-B (15 subjects)
 - AMI occurred 2-318 days following the last active injection, one event in the HEPLISAV group occurred within 30 days following the last active injection
 - Deaths due to cardiac events: 0.14% HEPLISAV (8 subjects), 0.11% Engerix-B (3 subjects)
 - There are no clinically significant differences in baseline cardiac medical characteristics between the two study groups
 - ISS: AMI reported in 0.17% HEPLISAV (17 subjects), 0.05% Engerix-B (2 subjects). Deaths due to cardiac events: 0.08% HEPLISAV (8 subjects), 0.10% Engerix-B (4 subjects)
- MAEs
 - The rate of MAEs between study groups was similar: 46.0% HEPLISAV, 46.2% Engerix-B
 - The rate of MAEs assessed as related and Grade 3 MAEs was similar between groups.
 - Herpes zoster was the only event reported in at least 0.5% HEPLISAV recipients (0.7%) and at at least twice the rate as in Engerix-B recipients (0.3%).
- Discontinuations due to MAEs
 - Excluding fatalities, early discontinuation from study treatment due to a treatment-emergent MAE was reported in 0.54% HEPLISAV (30 subjects), 0.50% Engerix-B (14 subjects) recipients.
 - Early discontinuation from study treatment due to an MAE assessed by the PI as related reported in 0.1% HEPLISAV (7 subjects), 0.2% Engerix-B (5 subjects)
 - HEPLISAV: migraine, diarrhea, hypoesthesia on face/paresthesia on face/nausea/vomiting/diarrhea, DVT, Bell's palsy, throat tightness/urticaria, and hypersensitivity

- Enderix-B: arthralgia/migraine/rash, rash, diarrhea, DVT, nausea/vomiting
 - An additional AE of urticaria reported 2 days following first injection with HEPLISAV, resulted in discontinuation of study treatment, and was assessed as unrelated.
- AESIs
 - Previous studies: HBV-16 was the only study which included prospective evaluation of potential immune-mediated events.
 - HBV-23 procedures: potential AESIs were referred to a specialist and reviewed by SEAC
 - Two experts in autoimmune disease and one infectious disease physician
 - Was the event is autoimmune? If so, was it new-onset and was it is related?
 - 61 subjects reported at least one potential new-onset AESIs or AIAEs – 0.70% HEPLISAV (39 subjects), 0.79% Enderix-B (22 subjects)
 - SEAC Assessments
 - No events were assessed as AI, new-onset, and related
 - AI and new-onset: 4 events in HEPLISAV – UC, alopecia areata, hypothyroidism, polymyalgia rheumatica; none in Enderix-B
 - SEAC could not confirm diagnoses: Rheumatoid Arthritis, Sjogren’s syndrome and Raynaud’s phenomenon, and Takayasu arteritis
 - Vasculitis or granulomatous disease
 - A 49 year-old Hispanic M subject in the HEPLISAV arm was diagnosed with Takayasu arteritis as an incidental finding on CT scan. It was assessed as most likely pre-existing by FDA consultants
 - A 43 year-old Hispanic F subject in the HEPLISAV arm with a history of bilateral ankle cellulitis for which she was hospitalized twice 2-3 months prior to study enrollment, reported a rash of her shins and forearms 69 days following second vaccination. A biopsy of her forearm demonstrated granulomatous dermatitis. Sarcoidosis was not ruled out.
 - Bell’s Palsy: 0.09% HEPLISAV (5 subjects), 0.04% Enderix-B (1 subject). Two subjects in the HEPLISAV group discontinued treatment due to the event; one was assessed as related.

- Day of onset following last active injection was 10-256 in HEPLISAV-recipients and day 27 in the Engerix-B recipient, with one HEPLISAV-recipient reporting an onset within 30-60 day window following vaccination.
 - Two of the HEPLISAV subjects had an another concurrent cranial nerve palsy: one with a sixth nerve palsy, one with a third nerve palsy that was attributed to diabetes.
 - Bell's palsy is estimated to occur in 13 to 34 per 100,000 per year (up to 0.034%).
 - ISS: 0.07% HEPLISAV (7 subjects), 0.05% Engerix-B (2 subjects)
- Thyroid events
 - Previous studies: In HBV-16, four events of hypothyroidism were identified in the HEPLISAV group, two determined to be new-onset.
 - Change in process for referral of events to SEAC in HBV-23
 - Thyroid MAEs 0.34% HEPLISAV (19 subjects), 0.43% Engerix-B (12 subjects)
- Venous thromboembolism (VTE)
 - Previous studies: Five cases of pulmonary embolism (PE) were reported in HEPLISAV recipients, including one fatality in a 46 year-old man without risk factors, compared to none in Engerix-B recipients.
 - HBV-23: Any VTE occurred 0.21% HEPLISAV (12 events in 12 subjects), 0.25% Engerix-B (9 events in 7 subjects). Three HEPLISAV recipients and two Engerix-B recipients reported PE.
 - Dynavax reports that, with the exception of one Engerix-B subject, all subjects reporting VTE had at least one factor predisposing them to hypercoagulation.
 - Lab sub-study
 - 207 HEPLISAV, 102 Engerix-B subjects in the laboratory substudy. Subjects were tested for genetic risk factors at baseline and for antiphospholipid antibodies at Weeks 0, 4, 8, 24, and 56.
 - Dynavax reports some differences between groups in some coagulation parameters at Week 8.
 - One subject with a positive thrombophilia work-up at baseline, reported an acute myocardial infarction complicated by an LV thrombus 64 days following second HEPLISAV injection, and 284 days following the second dose of HEPLISAV reported an additional event of LV thrombus and a PE.

- Renal events
 - Previous studies: Based upon repeat dose toxicity studies of the adjuvant in rats, showing diffuse proximal tubular degeneration, and limited follow-up periods in the previous clinical studies it was recommended that urinalyses, urinary microalbumin studies and serum chemistries be included in HBV-23. In the original ISS, there was one SAE of Renal failure in HEPLISAV groups and none in Engerix-B groups.
 - HBV-23: Acute Renal Failure (ARF) reported in 0.32% HEPLISAV (18 subjects, day of onset study day 47-391), 0.22% Engerix-B (6 subjects, study day of onset 48-301). ARF SAEs occurred in 4 HEPLISAV recipients and 3 Engerix-B recipients. Chronic renal failure reported in 0.21% HEPLISAV recipients, 0.11% Engerix-B-recipients.
 - Laboratory sub-study: Applicant reports no clinically significant differences between study groups in serum and urine indicators of renal function.

Data Integrity

- Several mistakes in their datasets and inconsistencies in AE reporting
 - This is increasing the time it takes to complete the review the data and additional inconsistencies may be identified through the course of the review.

Table 1. Deaths in HBV-23, Total Safety Population

Age	Sex	Cause of Death	Last Active Dose	AE Start (Days Since Last Active Dose)	Date of Death (Days Since Last Active Dose)	Related per PI	Alternative Plausible Cause per Reviewer
HEPLISAV							
Cardiac							
50	M	Acute coronary syndrome*	1	7	(b) (6)	N	Y
69	M	Acute myocardial infarction*	2	57		N	Y
57	M	Hypertensive heart disease	2	63		N	Y
62	M	Hypertensive heart disease*	2	212		N	Y
58	F	Hypertensive heart disease	2	225		N	Y
70	F	Cardiac arrest	2	243		N	Y
47	M	Myocardial infarction	2	287		N	Y
55	F	Cardio-respiratory arrest	2	298		N	Y
General							
61	F	Death – Unknown cause	2	59	N	Y	
51	F	Death	2	354	N	Y	

Age	Sex	Cause of Death	Last Active Dose	AE Start (Days Since Last Active Dose)	Date of Death (Days Since Last Active Dose)	Related per PI	Alternative Plausible Cause per Reviewer
Hepatobiliary							
68	M	Hepatic cirrhosis	2	27	(b) (6)	N	Y
Infectious							
56	M	Hepatitis C	2	35	(b) (6)	N	Y
Injury and Poisoning							
58	F	Victim of homicide†	1	1	(b) (6)	N	Y
49	M	Toxicity to various agents†	2	3	(b) (6)	N	Y
38	M	Toxicity to various agents†	2	36	(b) (6)	N	Y
62	M	Overdose†	2	88	(b) (6)	N	Y
44	M	Toxicity to various agents†	2	159	(b) (6)	N	Y
49	M	Toxicity to various agents†	2	160	(b) (6)	N	Y
42	F	Gunshot wound†	2	283	(b) (6)	N	Y
49	M	Accident†	2	286	(b) (6)	N	Y
Neoplasm							
49	M	Lung cancer metastatic	2	244	(b) (6)	N	Y
43	F	Small cell lung cancer metastatic	2	300	(b) (6)	N	Y
Nervous system							
46	F	Hypoxic-ischemic encephalopathy†	2	191	(b) (6)	N	Y
Respiratory							
67	M	Acute respiratory failure	2	15	(b) (6)	N	Y
61	M	Acute respiratory distress syndrome	2	120	(b) (6)	N	Y
Engerix-B							
Cardiac							
52	M	Myocardial infarction	1	12	(b) (6)	N	Y
48	M	Hypertensive heart disease	3	27	(b) (6)	N	Y
69	M	Cardio-respiratory arrest	3	88	(b) (6)	N	Y
Injury and Poisoning							
44	M	Cranio-cerebral injury†	1	17	(b) (6)	N	Y
55	M	Toxicity to various agents†	2	99	(b) (6)	N	Y
33	F	Head injury†	3	162	(b) (6)	N	Y
Neoplasm							
67	M	Pancreatic carcinoma metastatic	3	179	(b) (6)	N	Y

* Subject found dead. No autopsy performed.

† Events clearly due to overdose or injury.