

Record of Telephone Conversation - July 1, 2009 - Prevnar 13

System Info - 120983 SMITH, MICHAEL J 23-Feb-2010 20:31:27 SMITHM

RECORD OF TELEPHONE CONVERSATION

Submission Type: Original Application Submission ID: 125324/0 Office: OVRR

Product:

Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM197 Protein)

Applicant:

Wyeth Pharmaceuticals Inc.

Telecon Date/Time: 01-JUL-2010 12:30 PM Initiated by FDA? Yes

Telephone Number:

Communication Category(ies):

Advice

Author: JULIENNE VAILLANCOURT

Telecon Summary:

[Discussion of 6/30/2009 CBER comments on 6/11/2009 amendment to BLA \(#15\) on draft PVP](#)

FDA Participants: Marthe Bryant, Tina Khoie, Jingyee Kou, Douglas Pratt, Julienne Vaillancourt and Bob Wise

Non-FDA Participants: Bill Gruber, Dan Scott, Paul Coplan, Steven Bailey, Jay Graepel, Jennifer Schranz, Kim Center, Sharon Gray, Susan Urquhart, Roger Baxter (NCKP), John Hansen (NCKP), Jack Love and Carmel Devlin

Trans-BLA Group: No

Related STNs: None

Related PMCs: None

Telecon Body:

Record of Teleconference

Date/Time: July 1, 2009, 12:30 PM
File: BLA 125324
Product: Prevnar 13™
Sponsor: Wyeth Pharmaceuticals Inc.
Subject: Proposed Changes to Draft Pharmacovigilance Plans (PVP)
CBER Marthe Bryant, Tina Khoie, Jingyee Kou, Douglas Pratt, Julienne
Participants: Vaillancourt, Bob Wise
Wyeth Bill Gruber, Dan Scott, Paul Coplan, Steven Bailey, Jay Graepel,
Participants: Jennifer Schranz, Kim Center, Sharon Gray, Susan Urquhart, Roger
Baxter (NCKP), John Hansen (NCKP), Jack Love and Carmel Devlin
References: 1) June 11, 2009, Amendment to BLA (Modules 1.2, 1.11.3
and 5.3.5.2): response to Agency request Information, i.e.
response to 3/9/2009 CBER letter under IND --(b)(4)-,
regarding the draft PVP

2) June 30, 2009, 8:51 PM, E-mail, entitled "Comments for
July 1 Telecon on Draft PVP," from J. Vaillancourt to J. Love
and C. Devlin

Background

The purpose of this teleconference was to discuss the sponsor's proposed changes to the draft PVP, one component of the sponsor's post marketing plan for Prevnar 13. The original draft PVP included a proposal for a phase 4 safety study to be conducted at Northern California Kaiser Permanente (NCKP). Provided below as background for this teleconference is an up-to-date chronology of the development of the sponsor's post marketing plan for Prevnar 13.

Prevnar 13 Post Marketing Plan (PMP) - Chronology

12/12/2008 Submission to IND --(b)(4)- (amendment 199, serial 190): original draft pharmacovigilance plan (PVP) with post marketing vaccine effectiveness components.

1/12/2009 Teleconference: CBER provided comments to the sponsor on the draft PVP and followed up with written comments to the sponsor immediately afterward on the same day.

2/12/2009 Submission to IND --(b)(4)- (amendment 211, serial 201): response to CBER's 1/12/2009 comments on the draft PVP.

3/9/2009 Teleconference: CBER provided comments on the sponsor's 2/12/2009 response. The sponsor agreed to make various changes to the draft PVP, including the phase 4 safety study, based on the discussion.

3/31/2009 Original Application (i.e., submission of final rolling portion), BLA 125324. Submission included a draft Post Marketing Plan (PMP) with two components: a draft PVP and a draft plan to evaluate vaccine effectiveness post licensure. The components of the draft PMP reflected changes from the 12/12/2008 PVP submitted to IND --(b)(4)-, based on

- 6/3/2009** CBER's 1/12/2009 comments, but not on CBER's 3/9/2009 comments. Submission to IND --(b)(4)- (amendment 225, serial 215). Response to CBER's 3/9/2009 comments on the draft PMP, i.e., both PVP and vaccine effectiveness components. In addition a revised synopsis of study 6096A1-4002, the proposed phase 4 post marketing safety study, and a synopsis of the proposed phase 4 study to evaluate vaccine effectiveness against otitis media (OM) post licensure, were included.
- 6/11/2009** Response to CBER's 3/9/2009 comments on the draft PMP, i.e., both PVP and vaccine effectiveness components. In addition a revised synopsis of study 6096A1-4002, the proposed phase 4 post marketing safety study, and a synopsis of study 6096A1-4010, the proposed phase 4 study to evaluate vaccine effectiveness against otitis media (OM) post licensure, were included.
- 6/30/2009** CBER comments on information pertinent to proposed safety study 6096A1-4002 in the 6/3/2009 submission to IND --(b)(4)- and the 6/11/2009 amendment to BLA 125324 were sent to the sponsor via e-mail so that the sponsor might prepare for the teleconference scheduled for the following day.
- 7/1/2009** Teleconference: CBER's 6/30/2009 comments on the sponsor's recent response to the March 9, 2009, comments pertaining to proposed safety study 6096A1-4002 were discussed. [Note: it was agreed that discussion on other aspects of the PMP, e.g., proposed study 6096A1-4010, would be discussed at a later date, in a separate teleconference.]

July 1, 2009, 12:30 PM Teleconference Discussion

Discussion focused on the specific requests (page 3) in CBER's comments, provided to the sponsor on June 30, 2009. These specific requests are provided in italics below and followed by summarized discussion on each.

1. *OBE requests that you keep the 2 self-control windows.*

After much discussion back and forth between CBER and the sponsor concerning the pros and cons of maintaining the pre-vaccination self-control window (i.e., day -30 to -5 before 13vPnC vaccination), the sponsor agreed to maintain the pre-vaccination self-control window.

Of note, CBER noted that the pre-vaccination self-control window would provide the only control group for comparing rates of events in children who received the vaccine to those who did not. The sponsor agreed, but noted that this would be a valid comparison for dose 1 only. The sponsor also noted that use of such a control would introduce bias, such that any conditions that might preclude a patient from receiving the 13vPnC vaccine, e.g., suspected GBS, would not be seen at an expected rate in subjects in the pre-vaccination self-control group, because such subjects would not have received the vaccine. This might falsely elevate the rate of such events post vaccination. The sponsor noted that in the past they have looked at the rate of events in pre- and post vaccination windows, and considered

those events that occurred in both to be more important. The sponsor added that this was not ideal, because it was not clear what occurrence of an event in one window, but not in the other, really meant. The sponsor noted that overall the use of the pre-vaccination self-control window didn't seem to add any scientific value. CBER commented that a chief reason for being cautious in the pre-vaccination period, is that as a children age, their risks change. The sponsor suggested that this was a reason for not using the pre-vaccination self-control window. CBER concluded that both pre- and post vaccination self-control windows could be considered useful for all doses and advised the sponsor to provide a written justification for proposing not to use the pre-vaccination window. At this point the sponsor agreed to maintain the pre-vaccination self-control window.

2. *We request that you provide a tabulation of incidence rates with self-control comparative rates for pre- and post vaccination windows for all medically attended events for each setting and for all settings combined every three month.*

The sponsor commented that providing such data on all medically attended events for all settings every three months would not be logistically feasible. The sponsor noted that this would entail millions of events. CBER clarified that only medically attended events with a diagnosis were of interest. The sponsor noted that typically there are multiple diagnoses per visit. CBER clarified that the goal was not to see all AEs, but rather person-year tabulations of those events with the highest rates. The sponsor responded that in order to determine which AEs had the highest rates, all events would have to be looked at. CBER suggested that this could be done via programming a database search for all events with a rate $\geq 1\%$. The sponsor noted that it would not be possible to provide such information every three months, based on expected demand on programming time and resources. CBER then proposed that as a prospective interim analysis, the sponsor provide the incidence rates of prospectively specified AEs after so many doses of vaccine have been given, as an opportunity for CBER to see whether there are any preliminary signals. The sponsor agreed to consider this alternative approach for providing preliminary AE data from the study.

3. *OBE requests that the decision tree for comparison analyses on historical control be based not on statistical significance level of p-value of 0.05 but rather on a p-value of 0.1 (2-sided).*

The sponsor questioned CBER's rationale for this request. CBER noted that the intent was to err on the side of sensitivity balanced with feasibility, and thus a p-value of 0.1 was advised in order to prevent the analysis from being too restrictive. The sponsor suggested that multiple adjustments might be necessary. CBER commented that no multiple adjustments should be necessary for this analysis, because it was not a hypothesis-testing analysis.

The sponsor agreed to use a 0.1 p-value for the analyses using the pre- and post self control windows, but asked whether a p-value of 0.05 could be used for the historical control analysis. CBER responded that this would be acceptable as long as all findings from the historical control analysis are reported out, even if p-values are larger than 0.05.

4. *OBE requests that you provide causes of mortality for those infants who die within 2 months of vaccination..*

The sponsor agreed to do so.

5. *OBE requests that the comparison with historical controls be done on two distinct groups of infants, those who only received Prevnar 7 and those who started the series with Prevnar 7 and have received at least one dose of 13vPnC.*

CBER clarified that with regard to analysis of data using historical controls, CBER would request that comparisons be made against discrete and mutually excluding subsets of subjects. CBER noted, in particular, that subjects who received any combination of Prevnar/Prevnar 13 doses (i.e., 7,7,13 or 7, 13, 13), should be grouped together in the same comparison group. The sponsor agreed that all subjects receiving any mixed Prevnar/Prevnar 13 combination, regardless of combination, would be grouped into the same comparison group for analysis.

6. *High risk groups are defined as infants with sickle cell anemia, HIV, and airway constrictive diseases. Selections of such sub groups could be done based on the diagnosis or the corresponding medications. OBE asks that high risk expand to patients with steroids or other immunosuppressive medications.*

The sponsor explained that this would be difficult to do, because the dose and duration of such medication use (e.g., steroids) would not be known and could vary. The sponsor also noted that for some conditions such medications are administered in certain clinics. CBER asked whether system databases would have start dates for steroid medications. The sponsor explained that the pharmacy database could provide the dates for when such steroid medications were given. However, the sponsor was not sure whether the database could provide the dose and quantity for these medications. The sponsor noted that there is a separate immunosuppressive database.

7. *OBE requests that the line listing for children who are still in NCKP and did not complete the series during the study period be provided regardless of the status of other vaccination.*

The sponsor proposed providing line listings on two groups of subjects: 1) children who don't complete the Prevnar 13 series but complete at least one other routine vaccine series and 2) children who do not complete any series of routinely administered vaccines. The sponsor also proposed providing frequency distributions for ICD-9 codes for both groups. CBER asked whether this information could be provided on a quarterly basis. The sponsor proposed that this information be extracted from the databases once at one year after study initiation and reported to CBER at 18 months after study initiation.

8. *OBE asks that all vaccine providers be instructed to report all serious adverse events potentially related to the vaccine, regardless whether labeled or unlabelled.*

The sponsor agreed to do this.

9. OBE asks that the hypothesis testing analysis include all OBE's pre-specified diagnoses per utilization setting and for all settings combined.

The sponsor agreed to evaluate safety data for all pre-specified diagnoses as previously requested, including autoimmune diseases such as Kawasaki's disease. The sponsor agreed to submit this plan in writing as part of the study protocol.

10. CBER would expect this study to be initiated immediately following pending licensure and introduction of Prevnar 13, particularly given the limited scale of prelicensure safety data for this product. Thus, we consider it necessary to agree on the main outlines and detailed principles of the Phase 4 acute safety study prior to licensure. Submission of an advanced protocol no later than the first week of August would facilitate this goal.

The sponsor agreed to do so.

Action:

- The sponsor will submit a written response to CBER's June 30, 2009, comments to the BLA.
- The sponsor will provide an advanced draft protocol for the phase 4 safety study to the BLA no later than the first week of August.