

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
201023

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES-TEAM LEADER'S MEMO

NDA/Serial Number: NDA 201023/ SN 002

Drug Name: Cabazitaxel (XRP6258)

Indication(s): Treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel containing treatment regimen

Applicant: Sanofi-Aventis U.S. Inc.

Date(s): Submission date: 31 March 2010
PDUFA due date: 1 October 2010
Review completion date: 26 May 2010

Review Priority: Priority

Biometrics Division: Division of Biometrics 5 (HFD-711)

Primary Reviewer: Chia-Wen Ko, Ph.D.

Secondary Reviewers: Shenghui Tang, Ph.D., Team Leader

Concurring Reviewers: Rajeshwari Sridhara, Ph.D., Division Director

Medical Division: Oncology Drug Products (HFD-150)

Clinical Team: Amy McKee, M.D., Ian Waxman, M.D.,
John Johnson, M.D. & Amna Ibrahim, M.D.

Project Manager: Christy Cottrell

Keywords: hormone refractory prostate cancer, overall survival, superiority

This is an original New Drug Application (NDA) submission seeking the indication of cabazitaxel in combination with prednisone for the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel (Taxotere®) containing regimen. The applicant has submitted results from one pivotal study, EFC6193, “A randomized, open-label multi-center study of XRP6258 at 25 mg/m² in combination with prednisone every 3 weeks compared to mitoxantrone in combination with prednisone for the treatment of hormone refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen”. EFC6193 study protocol was reviewed and agreed by the Agency under a Special Protocol Assessment for demonstration of efficacy based on overall survival.

The pivotal trial met its study objective by showing a hazard ratio of 0.70 (95% confidence interval: 0.59-0.83, p<0.0001) for the experimental arm versus the control arm in overall survival. The median survival time was 15.1 months in the experimental arm compared to 12.7 months for patients in the control arm. Subgroup analyses showed consistent results in favor of cabazitaxel. There were no identified major statistical issues in efficacy analyses to prevent approval. For further details regarding the design, data analyses, and results of this phase 3 study, please refer to the statistical review by Dr. Chia-Wen Ko (May 26, 2010).

This team leader concurs with the recommendations and conclusions of the statistical reviewer (Dr. Chia-Wen Ko) of this application. The inference regarding favorable benefit-risk profile for the use of cabazitaxel in combination with prednisone in patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel (Taxotere®) containing regimen is deferred to the clinical review team.

(Please note that this is the updated version of the Team Leader’s Memo.)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

SHENGHUI TANG
05/26/2010

RAJESHWARI SRIDHARA
05/26/2010

NDA # / SN # Indication	Drug Name	Applicant	Submission Date	NDA Type
201023 / 0002 Metastatic prostate cancer which has progressed during or after a docetaxel-based therapy	Cabazitaxel (XRP6258)	sanofi aventis	31 March 2010	Original NDA

On **initial** overview of the NDA application for fileability: There are no filling issues - all necessary documents are available to allow statistical review to begin.

	Content Parameter	Yes	No	N/A	Comments
1	Is Index sufficient to locate necessary reports, tables, data, etc.?	X			
2	Are study reports including original protocols, subsequent amendments, etc. complete and available?	X			
3	Were safety and efficacy for gender, racial, and geriatric subgroups investigated (if applicable)?	X			<ul style="list-style-type: none"> • Only men were enrolled in the pivotal study • Age, race are reported as baseline patient characteristics • Safety analyses by race and subgroup analyses of OS by age were performed
4	Are data sets in EDR accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets)?	X			
5	Were ISS and ISE submitted?	X			ISS submitted. ISE is not required because the treatment efficacy will be evaluated based on a single study.
6	Designs utilized appropriate for the indications requested	X			
7	Endpoints and methods of analysis spelled out in the protocols	X			
8	Interim analyses (if present) planned in the protocol and appropriate adjustments in significance level made	X			An interim (futility) analysis of PFS was planned to be performed after 225 PFS events had occurred. The second interim analysis was added after a protocol amendment to be performed at the time of the 307 deaths (the 60% of the 511 deaths in the final analysis of the protocol) to assess the primary efficacy endpoint of OS based on the O'Brien-Fleming type I error spending function. The actual number of deaths at the second interim analysis was 365 instead of 307. Therefore, the type I error of the second and final analyses were adjusted according to the O'Brien-Fleming type I error spending function. The corresponding statistical significance levels for the interim analysis and the final analysis of OS were 0.0160 and 0.0452, respectively.
9	Appropriate references included for novel statistical methodology (if present)	X			
10	Sufficient data listings and intermediate analysis tables to permit a statistical review	X			
11	Intent-to-treat analyses	X			
12	Effects of dropouts on primary analyses investigated	X			Efficacy analyses repeated in PP population Censoring rule applied for time-to-event endpoints

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NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

CHIA-WEN KO
04/14/2010

SHENGHUI TANG
04/15/2010