Quick Minutes
Oncologic Drugs Advisory Committee Meeting
May 9, 2007

Summary Minutes of the Oncologic Drugs Advisory Committee
May 9, 2007:

The summary minutes for the May 9, 2007 meeting of the Oncologic Drugs Advisory Committee were approved on June 18, 2007.

I certify that I attended the May 9, 2007 meeting of the Oncologic Drugs Advisory Committee and that these minutes accurately reflect what transpired.

/s/
Johanna Clifford, M.Sc., RN

/s/
Maha Hussain, M.D., ODAC Chair

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Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA and from the sponsors. The meeting was called to order by Maha Hussaion, M.D.. (Committee Chair); the conflict of interest statement was read into the record by Johanna Clifford (Executive Secretary). There were approximately 150 persons in attendance.

Issue:

The Committee met to: (1) discuss new drug application (NDA) 22-092, mifamurtide, IDM Pharma Inc., proposed indication for the treatment of newly diagnosed resectable high grade osteosarcoma following surgical resection in combination with multiple agent chemotherapy and (2) NDA 22-062, proposed trade name ORBEC (beclamethasone dipropionate), DOR Biopharma, Inc proposed indication for the treatment of graft vs. host disease (GvHD) involving the gastrointestinal tract in conjunction with an induction course of high-dose prednisone or prednisolone.

Attendance:
Oncologic Drugs Advisory Committee Members Present (voting):
David Harrington., Ph.D., Pamela Haylock, RN (Consumer Representative), Maha Hussain, M.D.,(Chair), Joanne Mortimer, M.D., Michael Perry, M.D.,Ronald Richardson,M.D., Maria Rodriguez, M.D.

Oncologic Drugs Advisory Committee Consultants: (voting):
Peter Adamson, M.D., Susan Blaney (by phone), Ralph D'Agostino, Ph.D., Stephen George, Ph.D., Lee Helman, M.D., Angela Myers (patient representative), Gregory Reaman, M.D.

Industry Representative (non-voting):
Absent

Oncologic Drugs Advisory Committee Members Absent:
Ronald Bukowski, M.D., Alexandra Levine, M.D.,James Doroshow, M.D. Gary Lyman, M.D., S. Gail Eckhardt, M.D., Michael Link, M.D.

FDA Participants:
Richard Pazdur, M.D., Patricia Keegan, M.D., Patricia Dinndorf, M.D., Laura Lu, Ph.D., Mark Rothman, Ph.D.

Open Public Hearing Speakers:
Quynh-Tram Nguyen
Mattew Alsante, Executive Director, Sarcoma Foundation of America
Kurt Weiss, M.D.

The agenda proceeded as follows:

Sponsor Presentation	**IDM Pharma, Incorporated**
Unmet Need	Ian J. Lewis, M.B., ChB, FRCP, FRCPH Pediatric and Adolescent Oncologist St. James University Hospital, Leeds, UK
Product	Bonnie Mills, Ph.D. IDM Pharma, Inc.
Efficacy/Safety	Paul Meyers, M.D. Vice-Chairman, Department of Pediatrics Memorial Sloan-Kettering Cancer Center, NY

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Statistical Interpretation	Brent Blumenstein, Ph.D. Trial Architecture Consulting
Tolerability and Benefit/Risk	Eugenie S. Kleinerman, M.D. Professor and Head, Division of Pediatrics MD Anderson Cancer Center, TX
FDA Presentation	**NDA 22-092**
Medical Review	Patricia Dinndorf, M.D. Officer, Division of Biologic Oncology Products (DBOP), Office of Oncology Drug Products (OODP), FDA
Statistical Review	Laura Lu, Ph.D. Statistical Reviewer, Office of Biostatistics, CDER, FDA
	Questions from the Committee
	Open Public Hearing
	Questions to the ODAC and ODAC Discussion

ODAC Discussion:

Background

In order to obtain marketing approval, manufacturers demonstrate the substantial evidence of effectiveness of their products through the conduct of adequate and well-controlled studies. Substantial evidence is defined as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof." (sect 505 of the FD&C act)

In general, substantial evidence requires at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness. The requirement for more than one trial reflects the need for independent substantiation of the experimental results. Substantial evidence also may be provided by the results of a single adequate and well-controlled efficacy study when a single multicenter study of excellent design provides highly reliable and statistically persuasive evidence of an important clinical benefit, such as an effect on survival, such that a confirmatory is not ethical. In all cases, it is presumed that the single study has been appropriately designed, that the possibility of bias due to baseline imbalance, unblinding, post-hoc changes in analysis, or other factors is judged to be minimal, and that *the results reflect a clear prior hypothesis documented in the protocol*. (Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products; May 1998)

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The applicant submitted the results of INT 0133, a single study, in support of marketing approval. The study was a factorial design involving two chemotherapy regimens, one standard and one experimental, each studied with and without MTP-PE. The study arms were to be pooled for analysis of DFS **ONLY** if there was no interaction between the two experimental treatments. However, because there was an interaction, a pooled analysis is not valid. Pairwise comparisons (each experimental arm to the control arm, see table below) showed that no experimental treatment significantly improved DFS compared to the control regimen.

Variable	Number of Patients	Number of Events	Hazard Ratio relative to Regimen A	P-value[1]
Regimen A	171	60		---
Regimen A + MTP-PE	165	57	0.99	0.96
Regimen B	166	67	1.18	0.35
Regimen B + MTP-PE	169	46	0.73	0.11

[1] Cox regression analysis

Analysis of overall survival is considered exploratory because:

1) There was no prespecified plan for analysis of overall survival, and
2) All alpha (type 1 error rate) was spent in testing DFS.

In addition, there is substantial loss-to-followup for survival.

QUESTIONS TO THE COMMITTEE

1. Do the results of INT 0133 provide substantial evidence of effectiveness of mifamurtide (MTP-PE) in the treatment of patients with non-metastatic, resectable osteosarcoma receiving combination chemotherapy?

Vote: ***No – 12*** ***Yes – 2***

The committee felt overall that mifamurtide did show some revealing evidence in the overall survival study, but that the pooled data for disease free survival was problematic on a number of issues, noting statistical concerns in the qualitative versus quantitative data, concerns with exclusion criteria, issues concerning the current standard of therapy, dosing, asynchronous data documented in the CRFs submitted and insufficient follow up for late effects seen after treatment.

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SESSION II – AFTERNOON

Attendance:
Oncologic Drugs Advisory Committee Members Present (voting):
David Harrington, Ph.D., Pamela Haylock, RN (Consumer Representative), Maha Hussain, M.D. (Chair) Michael Link, M.D., Joanne Mortimer, M.D., Michael Perry, M.D., Ronald Richardson, M.D. Maria Rodriquez, M.D.

Oncologic Drugs Advisory Committee Consultants (voting):
Claude Sportes, M.D., Arthur Flatau (patient representative)

Oncologic Drugs Advisory Committee Members Absent:
Ronald Bukowski, M.D., James Doroshow, M.D., S. Gail Eckhardt, M.D., Alexandra Levine, M.D., Gary Lyman, M.D.,

FDA Participants:
Richard Pazdur, M.D., Robert Justice, M.D., Ann Farrell, M.D., Nancy Scher, M.D., Shan Sun-Mitchell, Ph.D., Rajeswari Sridhari, Ph.D.

Open Public Hearing
Sue Stewart, Executive Director, Blood and Marrow Transplant Information Network; Steve Dugan, Diane Pearl, Anna Pkhrikian-Kyrou, Philip McCarthy, M.D., Blood and Marrow Transplant Program, Roswell Park Cancer Institute, Steven Kanzer, Pipex, Inc.

The agenda proceeded as follows:

Sponsor Presentation	**DOR Bio Pharma, Incorporated**
Introduction and Background	Christopher J. Schaber, PhD President & Chief Executive Officer
orBec for the Treatment of Graft-Versus-Host Disease involving the GI Tract in Conjunction with an Induction Course of High-dose Prednisone or Prednisolone	George B. McDonald, MD Professor of Medicine University of Washington and Head, Gastroenterology/Hepatology Section Fred Hutchinson Cancer Research Center
FDA Presentation	**NDA 22-062**
Clinical Review	Nancy S. Scher, M.D. Medical Officer, Division of Drug Oncology Products (DDOP), OODP, FDA
Statistical Considerations	Shan Sun-Mitchell, Ph.D. Statistical Reviewer, Office of Biostatistics, CDER, FDA

Open Public Hearing

Questions from the Committee

Questions to the ODAC and ODAC Discussion

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ODAC Discussion:

This application contains two randomized clinical trials intended to demonstrate the efficacy and safety of BDP for the proposed indication.

The major study, ENT 00-02 was a phase 3, multi-center, randomized, double-blind, placebo-controlled trial of BDP in conjunction with an induction course of high dose prednisone in 129 patients with grade 2 GI GVHD following allogeneic transplant conducted from 2001 to 2005. The primary objective of this trial was to evaluate whether administration of BDP would decrease the time-to-treatment failure (TTF) through Study Day 50.

The supportive study, 875, was a single institution, randomized, double-blind, placebo-controlled, phase 2 trial conducted from 1994-1996 in 60 patients with GI GVHD post- allogeneic transplant. The primary objective of Study 875 was to evaluate the ability to increase oral caloric intake to 70% or more of the patient's estimated daily caloric requirements (ECR) at day 30.

Study ENT 00-02 failed to demonstrate an improvement for the primary endpoint of TTF at 50 days. Study #875 demonstrated that more patients who received BDP were able to achieve a daily oral caloric intake ≥ 70% of ECR at Study Day 30.

The Agency's findings with this application are:
1) The major trial designed to prove orBec's efficacy failed its primary endpoint. Therefore, any other analyses, whether based on pre-specified or unspecified secondary endpoints or the result of retrospective data collection, are exploratory and hypothesis generating. Additional analyses increase the probability of concluding a false positive result.

2) The major trial designed to prove orBec's efficacy had at least one imbalance (i.e., non-myeloablative transplants) between treatment arms. The impact of this imbalance is unknown.

3) The applicant's post-hoc proposal to combine data from the major trial and the supportive trial to demonstrate efficacy based on post-hoc analyses and endpoints is problematic because of differences between the trials and patient populations. Some concerns include:

- Trials had different primary endpoints and objectives
- Trials had different designs
- Changes in transplant procedures occurred during the 10 years between the start of the supportive trial and the completion of the major trial
- Changes in supportive care occurred during the 10 years between the start of the supportive trial and the completion of the major trial
- Trials had different dosing regimens/schedules.
- Neither study stratified for prior hematologic disease which could impact survival.

In addition, there are other regulatory considerations to consider regarding the sponsor's proposal to combine data.

According to the International Conference on Harmonization (ICH) Guidance E9: *"Under exceptional circumstances a meta analytic approach may also be the most appropriate way, or the only way, of providing sufficient overall evidence of efficacy via an overall hypothesis test. When used for this purpose the meta-analysis should have its own prospectively written protocol".*

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According to EMEA 2001 "Points to consider on applications with 1. Meta-analyses; 2. One pivotal study, Section II.1.3 Regulatory prerequisites of retrospective meta-analysis: *"Prerequisites for a retrospective meta-analysis to provide sufficient evidence for a claim include: - Some studies clearly positive"…"A retrospective meta-analysis of only two studies originally intended to stand on their own is not expected to add any useful information."*

The Agency would like the committee to address the following questions:

Question 1. Based on the data submitted, has substantial evidence of efficacy been demonstrated for orBec in the proposed patient population? (VOTE)

Vote: ***No – 7*** ***Yes - 2***

Question 2. If additional trials are required, discuss what would be the appropriate study population and randomization stratifications for future trials. Which endpoint(s) should be used to demonstrate clinical benefit? (DISCUSS)

The committee noted the limitations with the studies presented. The panel suggested that the sponsor may want to consider a trial designed to demonstrate that BDP can be used for prophylaxis against graft versus host disease..