Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Meeting of the Medical Imaging Drugs Advisory Committee
May 10, 2017

Location: FDA White Oak Campus, 10903 New Hampshire Avenue, Building 31 Conference Center, the Great Room (Rm. 1503), Silver Spring, Maryland

Topic: The committee discussed new drug application (NDA) 208-630 for 5-Aminolevulinic Acid Hydrochloride [5-ALA HCl], Powder, for oral solution, submitted by NX Development Corp., for the proposed indication as an imaging agent to facilitate the real time detection and visualization of malignant tissue during glioma surgery.

These summary minutes for the May 10, 2017, meeting of the Medical Imaging Drugs Advisory Committee of the Food and Drug Administration were approved on June 2, 2017.

I certify that I attended the May 10, 2017, meeting of the Medical Imaging Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/	/s/
Jennifer Shepherd, RPh	Henry D. Royal, MD
Designated Federal Officer, MIDAC	Chairperson, MIDAC

Summary Minutes
Medical Imaging Drugs Advisory Committee Meeting
May 10, 2017

The following is the final report of the Medical Imaging Drugs Advisory Committee meeting held on May 10, 2017. A verbatim transcript will be available in approximately four weeks, sent to the Division of Medical Imaging Products and posted on the FDA website at: https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/MedicalImagingDrugsAdvisoryCommittee/ucm553470.htm

All external requests for the meeting transcripts should be submitted to the CDER Freedom of Information Office.

The Medical Imaging Drugs Advisory Committee (MIDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on May 10, 2017 at the FDA White Oak Campus, 10903 New Hampshire Avenue, Building 31 Conference Center, the Great Room (Rm. 1503), Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and NX Development Corp. The meeting was called to order by Henry D. Royal, MD (Chairperson). The conflict of interest statement was read into the record by Jennifer Shepherd, RPh (Designated Federal Officer). There were approximately 50 people in attendance in the audience section. There were seven (7) Open Public Hearing speakers.

Issue:
The committee discussed new drug application (NDA) 208-630 for 5-Aminolevulinic Acid Hydrochloride [5-ALA HCl], Powder, for oral solution, submitted by NX Development Corp., for the proposed indication as an imaging agent to facilitate the real time detection and visualization of malignant tissue during glioma surgery.

Attendance:
MIDAC Members Present (Voting): David B. Hackney, MD; Peter Herscovitch, MD, FACP, FRCPC, FSNMMI; Paula M. Jacobs, PhD; Henry D. Royal, MD (Chairperson); Alicia Y. Toledano, ScD

MIDAC Members Not Present (Voting): Kimberly E. Applegate, MD; Wesley E. Bolch, PhD; Nicholas Dainiak, MD, FACP; Andrew D. Hardie, MD; Raymond Y. Kwong, MD, MPH

MIDAC Members Present (Non-Voting): Richard A. Frank, MD, PhD (Industry Representative)

Temporary Members (Voting): Peggy Almgren, RN (Patient Representative); Bonnie Arkus, RN (Acting Consumer Representative); Richard W. Byrne, MD; Mark R. Gilbert, MD; Donna R. Roberts, MD; Lucia J. Zamorano, MD

Guest Speakers: Cameron W. Brennan, MD

FDA Participants (Non-Voting): Charles J. Ganley, MD; Libero Marzella, MD, PhD; Nushin Todd, MD, PhD; Betsy Ballard, MD; Anthony Mucci, PhD

Designated Federal Officer (Non-Voting): Jennifer Shepherd, RPh

Open Public Hearing Speakers: Lloyd Zucker, MD; Al Musella, DPM (Musella Foundation for Brain Tumor Research & Information, Inc.); Georg Widhalm, MD, PhD; Jennifer Keenan Giliberto; Tucker Giliberto; Steven N. Kalkanis, MD (Henry Ford Hospital); Geri-Dee Shaffer (Southeastern Brain Tumor Foundation)

The agenda proceeded as follows:

Call to Order and Introduction of Committee	**Henry D. Royal, MD** Chairperson, MIDAC
Conflict of Interest Statement	**Jennifer Shepherd, RPh** Designated Federal Officer, MIDAC
Introductory Remarks	**Alex Gorovets, MD** Deputy Director Division of Medical Imaging Products (DMIP) Office of Drug Evaluation-IV (ODE-IV) Office of New Drugs (OND), CDER, FDA
GUEST SPEAKER PRESENTATION	
Neurosurgery for Brain Tumors: A General Overview	**Cameron W. Brennan, MD** Memorial Sloan Kettering Cancer Center
Clarifying Questions	
APPLICANT PRESENTATIONS	**NX Development Corp.**
Introduction	**Alan Ezrin, PhD** President and Chief Executive Officer NX Development Corporation
Visualization of Tumor During Glioma Surgery	**Constantinos G. Hadjipanayis, MD, PhD** Professor and Chair, Department of Neurosurgery Director of Neurosurgical Oncology Professor of Oncological Services Mount Sinai
Clinical Efficacy	**Walter Stummer, PhD, Dr med** Department of Neurosurgery University of Münster, Germany
Safety Results	**Walter Stummer, PhD, Dr med**

Benefit/Risk	**Constantinos G. Hadjipanayis, MD, PhD**
Conclusion	**Alan Ezrin, PhD**

Clarifying Questions

BREAK

FDA PRESENTATIONS

FDA Clinical Review	**Betsy Ballard, MD** Medical Officer DMIP, ODE-IV, OND, CDER, FDA
FDA Statistical Analyses	**Anthony Mucci, PhD** Mathematical Statistician Division of Biometrics I, Office of Biostatistics, Office of Translational Sciences, CDER, FDA

Clarifying Questions

LUNCH

OPEN PUBLIC HEARING

Questions to the Committee/Committee Discussion

BREAK

Questions to the Committee/Committee Discussion (cont.)

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** Discuss the efficacy outcomes used in this drug development program and their acceptability for substantiating the proposed claim. In your discussion, please consider each of the following points:

    a. The Applicant presented data demonstrating the intraoperative visualization of malignant tissue with the calculation of the percentage of visualized tissue fluorescence verified by histopathology (positive predictive value, or PPV). Please discuss the clinical significance of the provided PPV measurement of malignant tissue visualization with the use of 5-ALA and whether the provided data on malignant tissue visualization are sufficient for establishing efficacy of 5-ALA.

Committee Discussion:
Many committee members stated that PPV measurement is a useful measure to establish the efficacy of 5-ALA. Some committee members expressed concern over the false negatives; however, it was stated that this is to be expected when dealing with an infiltrative process. Please see the transcript for details of the Committee discussion.

b. Please discuss the potential clinical importance of the finding of non-fluorescent tissue samples being also positive for malignancy on histopathology.

Committee Discussion:
Several committee members stated that there is benefit to using the agent as 5-ALA allows a surgeon to remove more tumor, but that it is expected that some tumor will be left behind due to the nature of the disease. Please see the transcript for details of the Committee discussion.

c. One of the efficacy outcomes used by the Applicant is an improved completeness of resection defined on post-operative MRI enhancement. Please discuss the clinical importance of a "complete resection" in the setting of glioma surgery and comment on the clinical meaningfulness of using post-operative MRI to measure the completeness of resection.

Committee Discussion:
The committee members stated that there are imperfect tools to determine the completeness of resection; however the more complete the resection, the better the prognosis and post-operative follow up of the patient will be. One committee member stated that leaving tumor behind complicates following the patient as you are more likely to see pseudo-progression. Please see the transcript for details of the Committee discussion.

d. In assessing the totality of evidence of the potential benefit of 5-ALA, please comment on the clinical significance, if any, of the observed improvement in progression free survival and of the lack of improvement in overall survival. In your discussion please comment on the following:
    i. Whether either should be mentioned in the prescribing information if 5-ALA is approved for marketing in the U.S.
    ii. How the outcome of progression free survival could relate to potential assessment of patient reported outcomes (PROs) and what type of PROs would be relevant to this setting.

Committee Discussion:
Several committee members stated that progression free survival and overall survival should not be mentioned in the prescribing information. It was also stated that the sponsor should be encouraged to collect patient reported outcomes (PROs), but not required to do so. Please see the transcript for details of the Committee discussion.

2. **DISCUSSION:** Please discuss possible risks associated with increased resection, e.g. the potential for increased neurological deficits

a. Please discuss any other safety concerns you might have about this drug.

Committee Discussion:
Two committee members stated that they did not have concerns about the safety of 5-ALA, but that it is important to stress that standard surgical judgment needs to be used when evaluating the different levels of tumor fluorescence. It was also stated that there is some risk in going astray in mildly positive areas, but that surgeons are trained to evaluate risk in eloquent vs. ineloquent areas of the brain. One committee member stated that the labeling should not contain any language that indicates that 5-ALA delineates tumor tissue from normal brain tissue. Another committee member stated that the labeling should caution prescribers that using 5-ALA in eloquent areas is particularly risky and that standard surgical principles should be applied. Please see the transcript for details of the Committee discussion.

3. **VOTE:** Do you recommend the approval of 5-ALA for the proposed indication as an imaging agent to facilitate the real time detection and visualization of malignant tissue during glioma surgery?

YES 11 NO 0 ABSTAIN 0

Committee Discussion:
The committee voted unanimously in favor of approval of 5-ALA for the proposed indication as an imaging agent to facilitate the real time detection and visualization of malignant tissue during glioma surgery. Many committee members stated that the data presented was enough to provide a favorable benefit/risk ratio that would support an approval. Several committee members also stated that 5-ALA would be a valuable additional tool in the surgeon's armamentarium. One committee member said that the use of 5-ALA may reduce the need for the use of intraoperative MRI and may provide an additional level of confidence for the surgeon that may allow for a faster surgery. Please see the transcript for details of the Committee discussion.

The meeting was adjourned at approximately 2:45 p.m.