

**MEDICAL IMAGING DRUG  
ADVISORY COMMITTEE  
(MIDAC)**

**5-aminolevulinic acid hydrochloride (5-ALA)**

**NDA 208630**

**ALEX GOROVETS, MD**

**DEPUTY DIRECTOR**

**DIVISION OF MEDICAL IMAGING PRODUCTS**

**CDER/FDA**

**May 10, 2017**

# NEW DRUG APPLICATION

- OPTICAL IMAGING AGENT
- MALIGNANT GLIOMA
- INTRA-OPERATIVE USE
- VISUALIZATION OF MALIGNANT TISSUE
- APPLICANT: NX DEVELOPMENT CORP.

# REGULATORY CONSIDERATIONS

- Pharmacologic Class: Optical Imaging Drug
- Imaging Guidances 2004
- Developing Medical Imaging Drug and Biological Products Part 2: Clinical Indications
- Clinical Utility / Value
- Performance / Accuracy

# SAFETY AND EFFECTIVENESS

- Statutory Standards - 21 U.S. Code § 355 (d)
- 21CFR314.125
- Substantial evidence
- Adequate and well-controlled investigations
- 21CFR314.126

# Adequate and Well-Controlled

- Design: valid comparison with a control
- Concurrent Controls: placebo, dose-comparison, no-treatment and active-treatment
- Bias Minimization
- Randomization
- Blinding

# Approval of an Application

- Uncontrolled studies are not acceptable as the sole basis for the approval
- 21CFR314.105 – approval of an application- after the drug meets the statutory standards
- Many drugs and the wide range of uses demand flexibility
- FDA is required to exercise its scientific judgment to determine the kind and quantity of data

# NDA 208630

- Orphan Designation; Priority Review
- 505 (b) (2): three studies and 12 publications
- Primary Efficacy Endpoint:  
Positive Predictive Value (PPV)
- Proposed Indication: *to facilitate the real time detection and visualization of malignant tissue during glioma surgery* – a “visualization” claim

# CLINICAL OUTCOMES

- EXTENT OF RESECTION
- SURVIVAL
- PATIENT REPORTED OUTCOMES
- CONTROLLED CLINICAL OUTCOMES DATA
- DIAGNOSTIC IMAGING CLAIM





# QUESTIONS

# QUESTION 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:

# QUESTION 1 (cont.)

- 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.

## QUESTION 1 (cont.)

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

# QUESTION 1(cont.)

- 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.

## QUESTION 2

### DISCUSSION:

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

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

## QUESTION 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?





# **Medical Imaging Drugs Advisory Committee Meeting**

## **5-Aminolevulinic Acid (New Drug Application 208630)**

### **Clinical Review**

**Betsy Ballard, MD FACS  
Division of Medical Imaging Products  
Office of Drug Evaluation IV, Office of New Drugs, CDER, FDA  
May 10, 2017**

## Proposed Indication

*Indicated as an imaging agent to facilitate the real time detection and visualization of malignant tissue during glioma surgery*

## Proposed Dose

20mg/kg single dose administered orally 2-4 hours prior to surgery

# Indications for Imaging Agents

- Developing Medical Imaging Drug and Biological Products: Part 2 Clinical Indications
  - Structure delineation (visualization)
  - Disease or pathology detection or assessment
  - Functional, physiological, or biochemical assessment
  - Diagnostic or therapeutic patient management

# Requirements for Drug Approval



- Substantial evidence is defined in section 505(d) of the Act as “evidence consisting of adequate and well-controlled investigations”
- Generally requires two adequate and well-controlled studies, each convincing on its own, to establish effectiveness
- However, based on relevant science, data from one adequate and well-controlled clinical investigation may be sufficient to establish effectiveness

# Approval of Medical Imaging Agents



- Simply generating an image, for which the implications to the patient are not understood, does not confer benefits to the patient
- Therefore, establishing effectiveness of a medical imaging agent requires data and other information on:
  - precision and accuracy and
  - clinical value

# Approval of Medical Imaging Agents

- A medical imaging agent needs to provide accurate and reliable information that facilitates clinical management e.g.
  - helping make an accurate diagnosis
  - contributing to beneficial clinical outcome
- The usefulness of an imaging agent may be self-evident. Clinical usefulness can generally be established by:
  - direct demonstration in clinical studies
  - reference to historical data

# What Clinical Outcomes Could Support Clinical Benefit?

An agent designed to enhance visualization of tumor cells may require supportive evidence of clinical usefulness such as:

- Extent of tumor resection
- Patient survival
- Patient function

# Clinical Review Approach

- A preliminary assessment showed insufficient evidence for indications of improved clinical outcomes (e.g. Progression Free Survival, Overall Survival)
- The focus of the application is on evidence needed for the indication of improved visualization based on concordance between histopathology and tissue fluorescence
- The clinical outcome data will be examined to support the value of improved visualization



# Overview of FDA Presentations



## Clinical

- Efficacy: clinical outcome endpoints, literature reports
- Safety: clinical studies and post-marketing experience

## Statistical

- Evidence for visualization indication
  - Positive Predictive Value, False Negative Rate
  - Other exploratory analyses

NDA 208630

# **EFFICACY**

# Sources of Data

- Two phase 2, one phase 3 study
  - ALS-28, ALS-30, ALS-3
  - Studies included patients with newly diagnosed and recurrent disease
- Clinical study safety database of 550 patients
- Review of literature

# Common Study Characteristics

## ALS-28, ALS-30, ALS-3

- After biopsies were taken, the surgeon assessed extent of resection
  - Did the remaining residual fluorescence appear abnormal under White Light (WL)
  - Described anatomical area of remaining tumor
  - Estimated volume of remaining tumor
  - This design did not allow for adequate control of ascertainment bias
- Central neuropathological and neuroradiologic assessments blinded to treatment



# Common Study Characteristics

## ALS-28, ALS-30, ALS-3

- Patients with newly diagnosed, contrast enhancing brain lesions; Study ALS-30 included patients with recurrent tumor
- Tumor grade was generally not known at study entry

# ALS-3

## Study Protocol (1999-2004)

- Prospective, randomized, multicenter, phase 3
- **Controlled:** white light vs fluorescence
- Study Endpoints:
  - Completeness of resection = % patients without contrast enhancement on post-operative MRI
  - Progression Free Survival (PFS) at 6 months

# ALS-3 Biopsy Region Selection

- Resection performed with both white light (WL) and fluorescent Light (FL)
- Geographic assignment of biopsy regions
  - Tumor core
  - Tumor margin
  - Distant
- Assessment of these areas as to the intensity of fluorescence

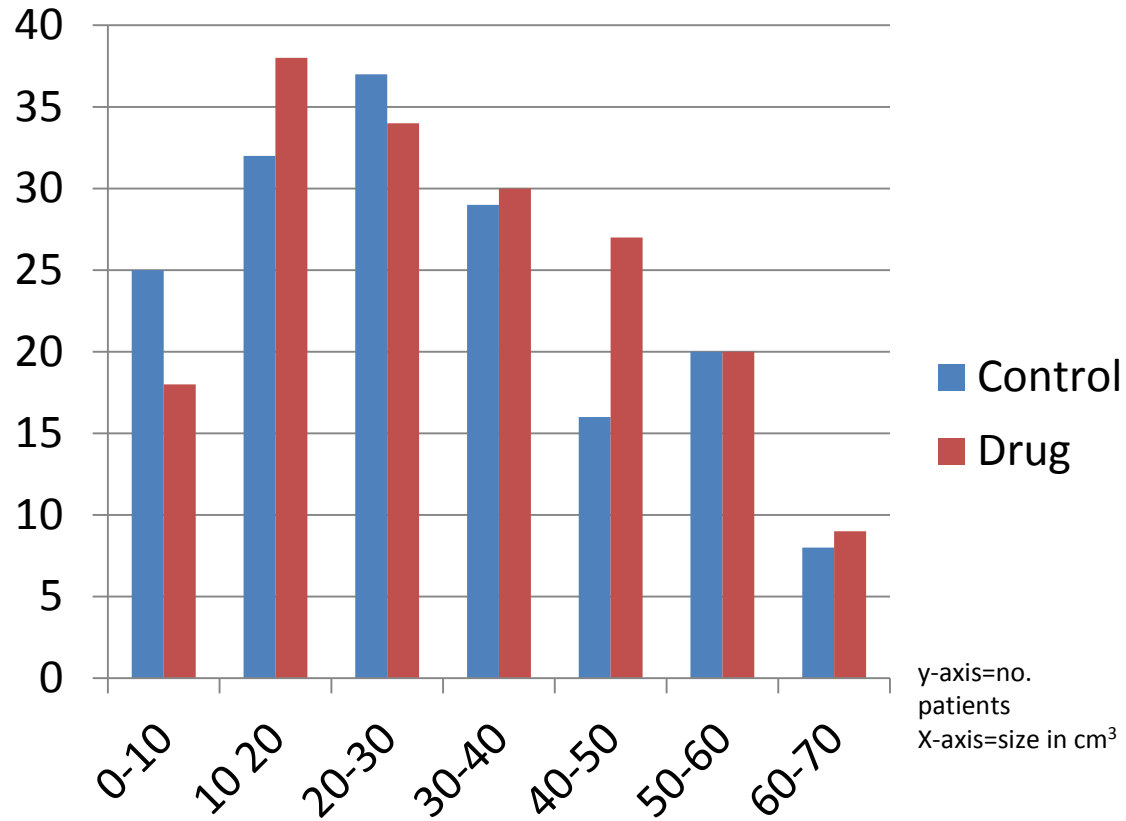
NDA 208630

# EXTENT OF TUMOR RESECTION



# Extent of Tumor Resection

- Glioblastomas infiltrate across white matter beyond radiographically and clinically evident primary masses. The surgical procedure is a “debulking” of tumor rather than a resection with clear margins
- Factors influencing resection
  - Tumor size, location, proximity to eloquent areas
- Assessment of resection
  - post-operative (72 hours) MRI defined as absence of residual contrast accumulation
  - “Complete” resection by MRI does not equal histological absence of tumor



## Tumor Volume by Study Arm ALS-3

Similar distribution of tumor size across two arms

	Localization		Speech	Motor	Optical
FL	Eloquent	111	28	54	31
	Non-Eloquent	66			
	Unknown	8			
Control (WL)	Eloquent	99	39	41	16
	Non-Eloquent	85			
	Unknown	16			

### Localization of Tumors in ALS-3

All tumors were deemed resectable on pre-operative MRI

# “Completeness” of Resection

	5-ALA	Control	Difference (95% CI)
<b>ALS-3</b>	112/176 (64%)	65/173 (38%)	26% (16%, 36%)

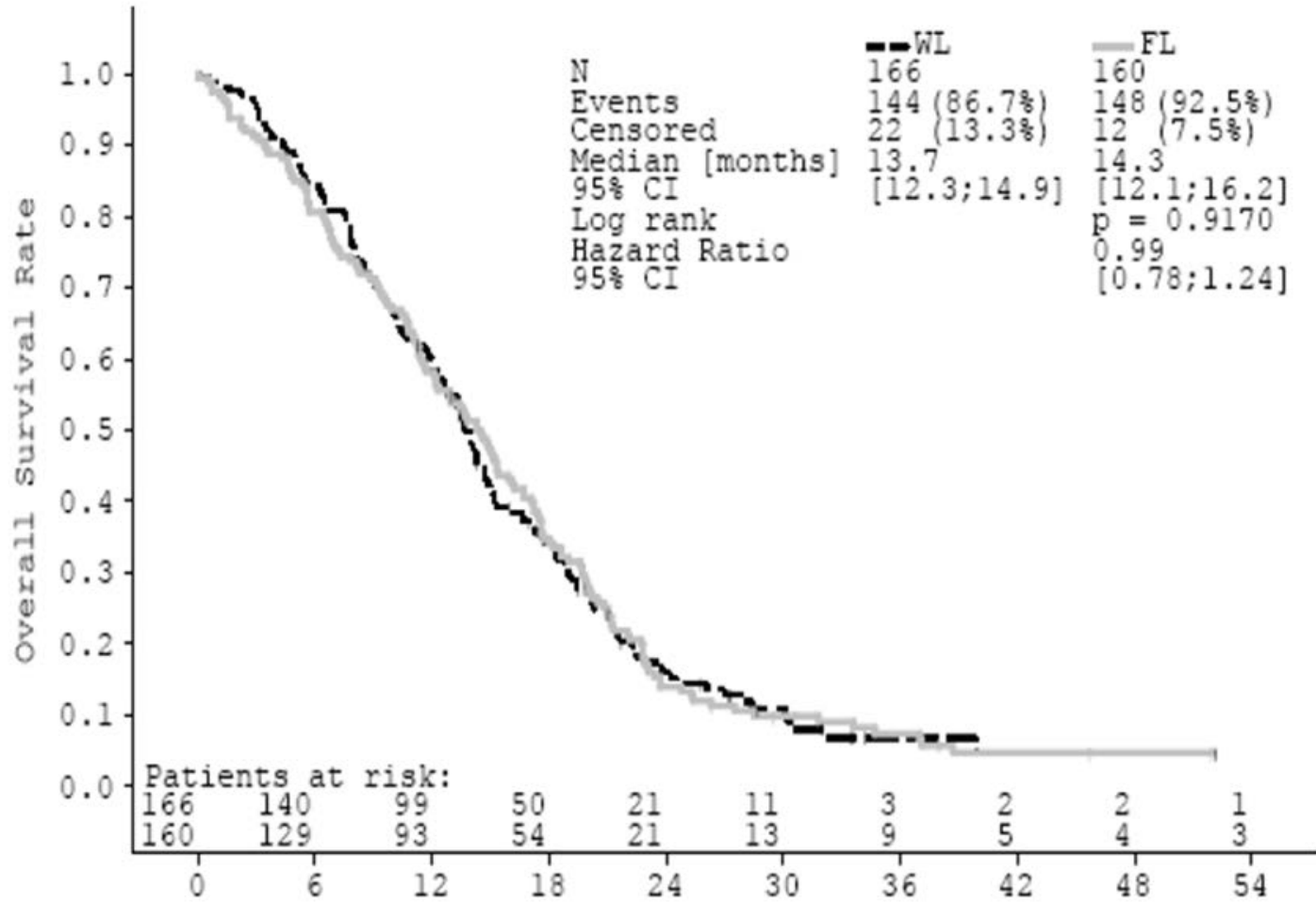
NDA 208630

# PATIENT SURVIVAL

# Patient Survival

- Progression free survival (PFS) and overall survival (OS) are affected by subsequent patient management
- Patients were to receive standard radiation and chemotherapy post-operatively but not all did
- Tumor progression defined as occurrence of new tumor or increase in volume of residual tumor > 25% on MRI
- PFS: 36% (5-ALA) vs. 22% (WL)

# Overall Survival – Kaplan Meier estimates



Sponsor Data

NDA 208630

# **ADDITIONAL LITERATURE SUPPORT**



# Methodology for Literature Selection



- Publications on 5-ALA use for glioma resection must have reported
  - biopsy-based PPV
  - surgeon's assessment of fluorescence during resection
  - resection completed under white light prior to fluorescence; or surgeon switched between the two

# Literature Studies Selected

- 11 single-arm, prospective studies
  - 2 required complete resection under WL followed by FL
  - 6 allowed surgeons to switch as desired
  - 3 had no mention of how the fluorescence was used
- Patients with primary or recurrent tumors
- 5-ALA used in conjunction with other intra-operative assessment methods

# Results of Supportive Literature



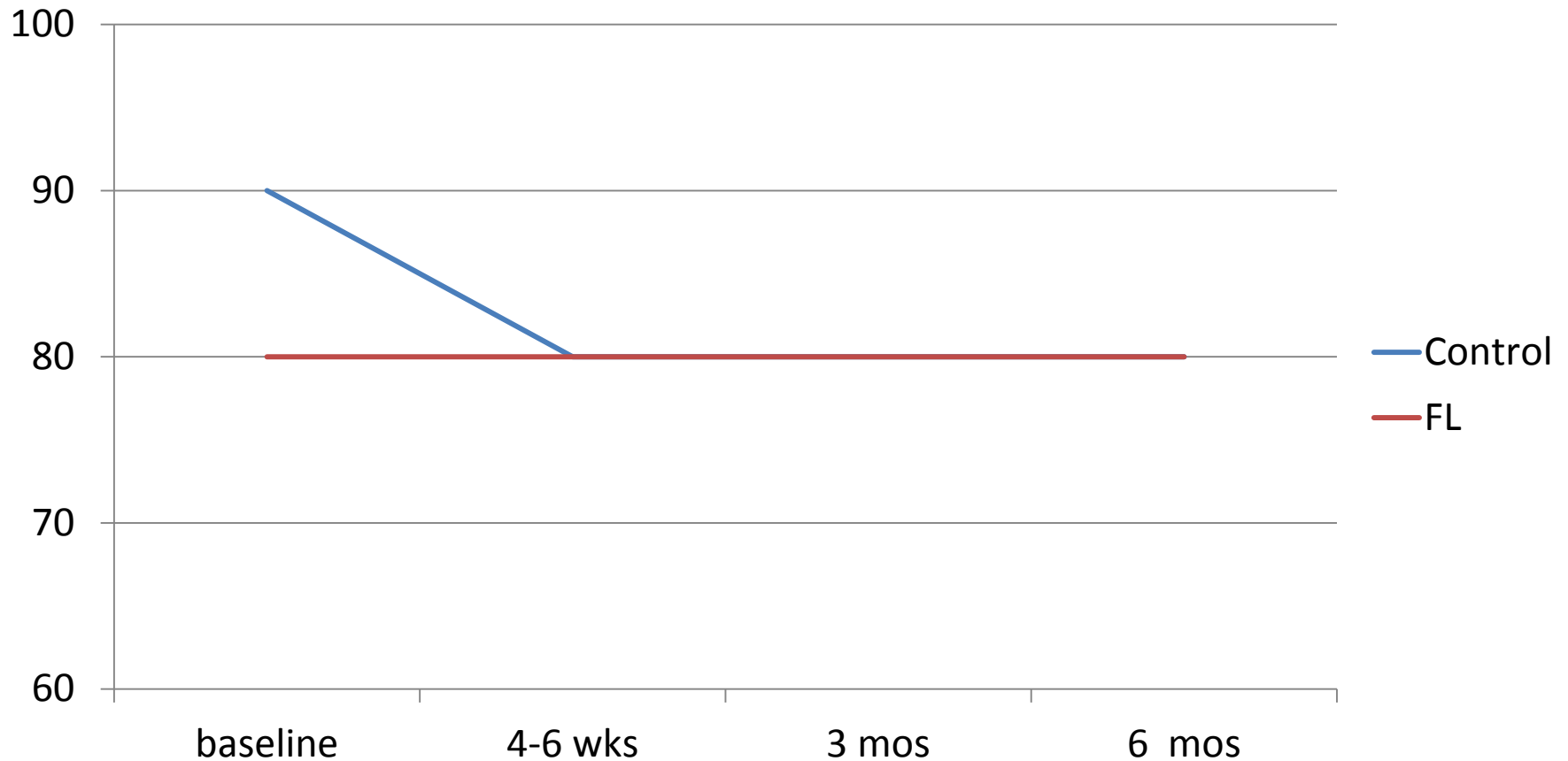
Study	No. Patients	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Stummer et al (2000)	52	89	96	99	50
Roberts et al (2011)	11	75	71	95	26
Panciani et al (2012)	41	91	89	89	91
Coburger et al (2014)	34	91	80	99	22
Hauser et al (2016)	12	81	43	96	12.5
Diez Valle et al (2011)	36	91	89	100 (S) 97 (W)	66
Ewelt et al (2011)	30	71	92		
Iodate et al (2011)	30	100 (S) 89 (W)		100 (S) 97 (W)	67
Lau et al (2015)	59	82	65	93	38
Valdes et al (2010)	3	50	100	100	20



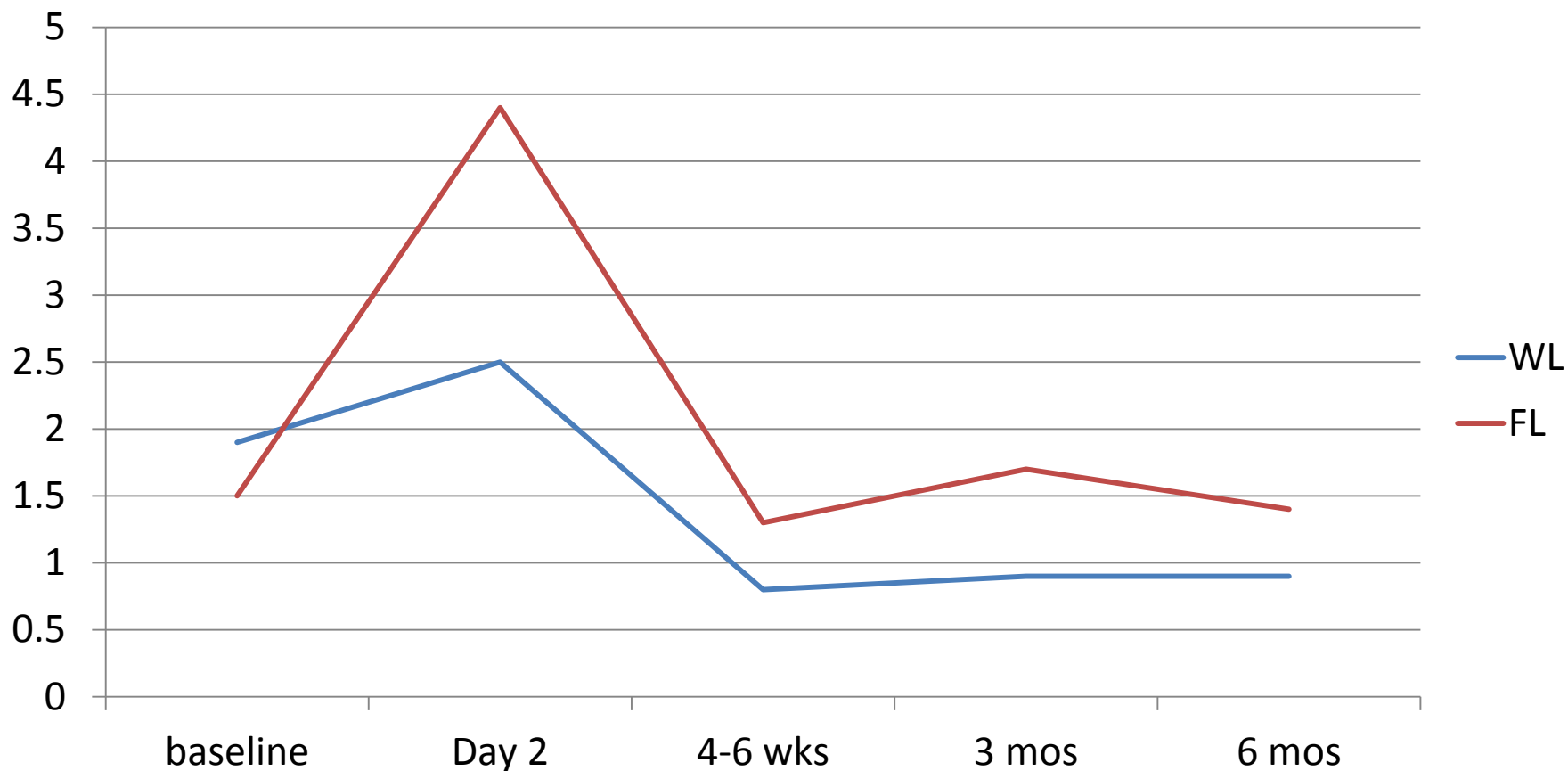
NDA 208630

# PATIENT FUNCTIONAL OUTCOMES

# Karnofsky Performance Scale Over Time



# NIH Stroke Scale Over Time



NIH Stroke Scale: Assessment of motor, sensory, speech, neurological signs  
Scale rates from 0-36

NDA 208630

# SAFETY EVALUATION

# Safety Assessments

- The data base for the safety analysis derived from 5 studies: ALS-8, ALS-28, ALS-30, ALS-3 and ASL-32
- Drug related adverse reactions
- Procedure related adverse reactions



# Studies for the Safety Assessment

**ALS-8:** Single center, dose- finding study, uncontrolled. N=21

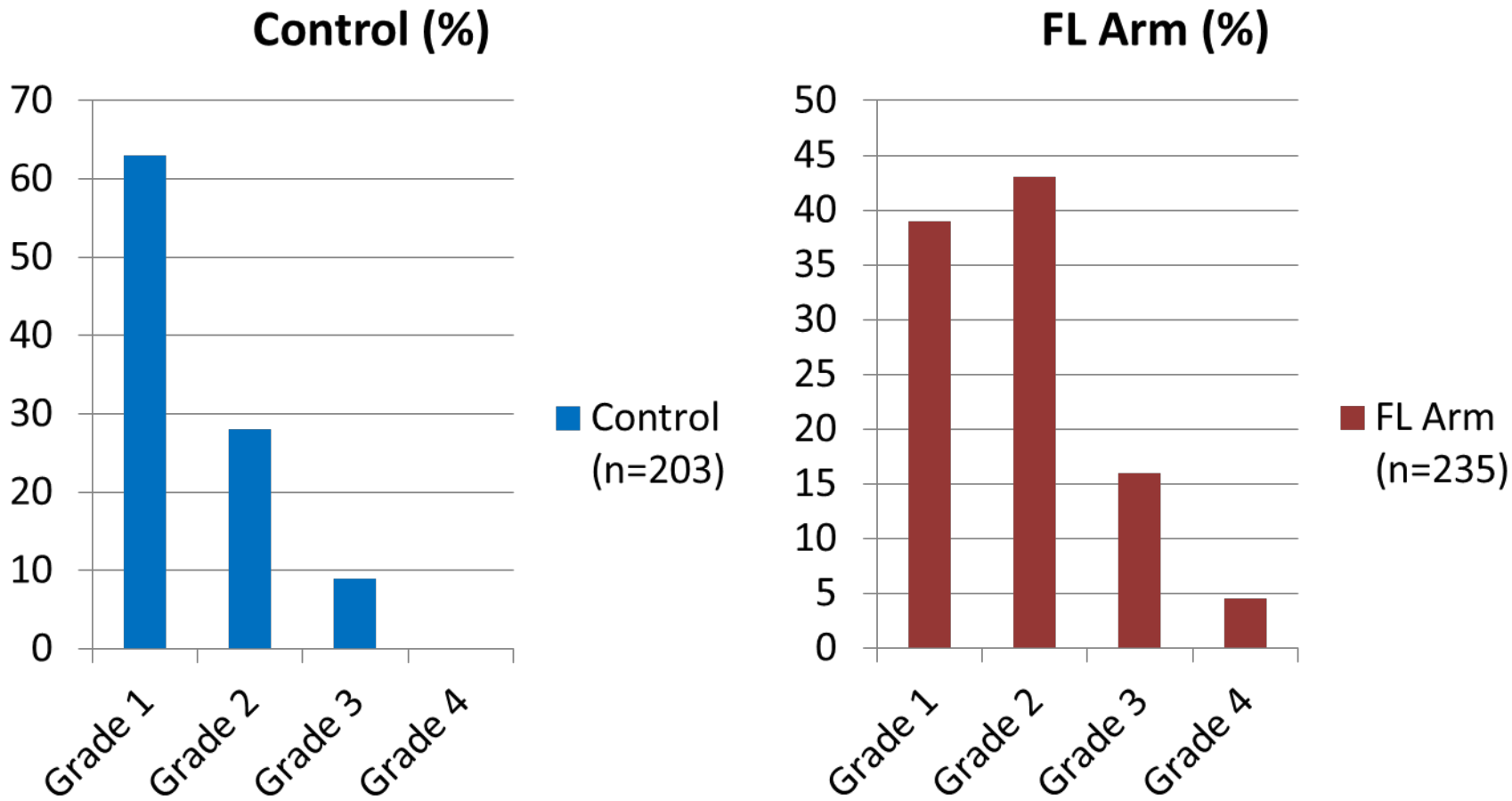
**ALS-32:** Prospective, single-arm, multicenter, uncontrolled. N=243

# Summary of Adverse Reactions



	ALS-8	ALS-28	ALS-30	ALS-3		ALS-32	Total
				Drug	Control		
<b>No. of events</b>	134	92	48	281	254	279	954
<b>Deaths</b>	0	2	17	16	19	7	44
<b>Serious Events (Grades 3-4)</b>	10	16	5	19	27	76	143
<b>Adverse Events (Grades 1-2)</b>	120	65	43	184	208	203	703

# ALS-3 Adverse Reactions by Severity



# Drug Related Adverse Reactions



- Photosensitivity, photodermatitis
- GI: nausea, diarrhea
- Hypotension, hypertension
- Transient elevation of liver function tests
- Pyrexia

# Procedure Related Adverse Reactions



- Thromboembolic events
- Cardiac, Hematologic
- Pulmonary
- Infectious
- Neurologic:
  - Motor deficits
  - Visual deficits
  - Speech disorders
  - Brain edema
  - Seizures
  - Transient alterations in cognitive function

# Neurologic Deficits



Neurological Serious Adverse Events	ALS-8	ALS-28	ALS-30	ALS-32	ALS-3 Treated	ALS-3 Control
Convulsions/Seizures	2	3	1	12	36	25
Altered Level of Consciousness	1		1	1	1	2
Ataxia	0	1	0	0	11	6
Aphasia	1	8	7	19	24	12
Dysarthria/Speech	1	3		3	15	15
Hygroma				3	1	1
Cerebral Hemorrhage	0	1	0	2	4	3
Facial Nerve Paralysis/Nerve Palsies	3		3	5	7	11
Hemiparesis/Hemiplegia	3	8	8	38	24	21
Hemianopsia	7	5	4	6	23	8
Cerebral Infarction	0	2	0	3	1	
Cerebral Edema				2	0	3
Somnolence/Confusion		3			4	3
Hydrocephalus		1			1	2
Dizziness	0	2	0	0	2	4
Headache	5	4		8	12	11
Totals	45	40	24	103	165	116



# Periodic Safety Update

- Submitted in 2015
- Estimated cumulative patient number receiving the drug is 58,413
- No reports of unanticipated adverse reactions

# 5-ALA Training Program

The applicant proposes a training program for neurosurgeons prior to using 5-ALA. The program:

- provides information on techniques to optimize the use of 5-ALA fluorescence guided surgery
- **does not** mitigate a drug risk
- is not being considered as a Risk Evaluation and Mitigation Strategy (REMS)



# Conclusions

- The patient outcome data generally are supportive of the proposed visualization indication
- Data from the publications provide descriptive information on the visualization performance of 5-ALA
- Safety profile of 5-ALA is generally acceptable for its proposed clinical use

# **Medical Imaging Drugs Advisory Committee Meeting**

May 10, 2017

**5-Aminolevulinic Acid  
(New Drug Application 208630)**

## **FDA Statistical Analyses**

Anthony Mucci, PhD

Mathematical Statistician

Division of Biometrics I/Office of Biostatistics

Office of Translational Sciences/CDER/FDA

# Outline

- Studies under Statistical Review
- Overview of Study Designs
- Positive Predictive Value (PPV) and Fluorescence False Negative Rate (FNR-FL)
- Exploratory Analyses
- Concluding Remarks

NDA 208630

# STUDIES UNDER STATISTICAL REVIEW

# Studies under Statistical Review

**Focus: Three Prospective Studies**  
**Focus on Statistical Estimation**

Study28: MC-ALS.28/GLI: Phase 2, prospective, single arm, uncontrolled, multicenter study  
(Conducted 10/2002 to 6/2004)

Study30: MC-ALS.30/GLI: Phase 2, prospective, single arm, uncontrolled, multicenter study  
(Conducted 6/2003 to 9/2005)

Study03: MC-ALS.3/GLI: Phase 3, prospective, randomized, group-sequential, MRI-rater-blinded, controlled, multicenter study  
(Conducted 10/1999 to 7/2004)

NDA 208630

# OVERVIEW OF STUDY DESIGNS

# Overview of Study Designs



## Study ALS-28 (Phase 2)

### Primary Inclusion Criterion:

- Patients with a **newly diagnosed** unilocular malignant glioma for whom surgery was indicated
- histopathological verification that resected tissue was III/IV glioma
- **N = 36 patients**

### Surgical Protocol:

- Tumor resection under White Light (WL)
- Biopsies of Non Fluorescent (Non-FL), Weakly Fluorescent (Weak FL) , and Strongly Fluorescent (Strong FL) tissues
- Intention was to obtain 2 Non-FL, 3 Weak FL, and 3 Strong FL
- **Median FL = 6 ; Median Non-FL = 4**

# Overview of Study Designs

## Study ALS-28

### Post-Surgical:

- Biopsied tissue was classified as Positive/Negative by Central Histology
- Completeness of resection was determined by Central Read of an early post-surgical MRI

### Endpoints for Estimation:

- Primary: Patient Level PPV = % of patients *all* of whose FL biopsies were Histology Positive
- Secondary: Biopsy Level PPV = % Histology Positives among FL biopsies



# Overview of Study Designs



## Study ALS-30 (Phase 2):

### Primary Inclusion Criterion:

- Patients with **recurrence** of a unilocular malignant glioma for which surgery was indicated
- Histopathological verification that resected tissue was Grade III/IV glioma
- **N = 33 patients**

### Surgical Protocol:

- Tumor resection under White Light (WL)
- After resection two areas were chosen for collection of biopsies by surgeon:
  - Area#1 was a WL area classified as normal; Area#2 was a WL area classified as Abnormal
- FL was then engaged for acquisition of Strong FL biopsies and Weak FL biopsies
- **Very few Non-FL biopsies were acquired**
- **Median FL = 11**

### Post-Surgical:

- Biopsied tissue was classified as Positive/Negative by Central Histology
- Completeness of resection was determined by a Central Read of an early post-surgical MRI

### Endpoints for Estimation:

- Primary: Patient Level PPV = % of patients *all* of whose FL biopsies were Histology Positive
- Secondary: Biopsy Level PPV = % Histology Positives among FL biopsies

# Overview of Study Designs



## Study ALS-3 (Phase 3)

### Primary Inclusion Criterion:

- Patients with a unilocular malignant glioma for which surgery was indicated
- Histopathological verification of III/IV glioma
- **N = 346 patients**

### Pre-Surgical:

- Patients were randomized (1:1) to the 5-ALA (FL) Fluorescence Arm or to White Light (WL) Control Arm;
- **Surgeons could not be blinded to type of light (FL or WL)**

### Surgical Protocol:

- In 5-ALA (FL) Arm, and prior to resection, 3 areas were chosen for biopsy acquisition:
  - tumor core ; tumor margin ; distant
- FL was employed for FL classification of biopsies from these areas: Non-FL, Weak FL, Strong FL
- **Mean FL = 2, Mean Non-FL = 1**

# Overview of Study Designs

## Study ALS-3



### **Post-Surgical:**

- Biopsied tissue was classified as Positive/Negative by Central Histology
- Completeness of resection was determined by a Central Read of an early post-surgical MRI
- Progression-Free Survival (PFS) was evaluated at various times ( most critical at 6 months)

### **Endpoints for Estimation and Hypothesis-Testing:**

- Primary#1: % Patients with Complete resection on early Post-surgery MRI
- Primary#2: % Patients who were Progression-Free at 6 months post-surgery

NDA 208630

**POSITIVE PREDICTIVE VALUE (PPV)  
FLUORESCENCE FALSE NEGATIVE RATE  
(FNR-FL)**

# Positive Predictive Value (PPV)



## Primary Endpoint

**Primary Endpoint:**

**Biopsy PPV = % FL histology Positive biopsies**

**FDA exploratory analyses for estimation**

- Alternative forms of PPV (defined on the next slides)
- A complementary endpoint: Biopsy-level Fluorescence False Negative Rate (FNR-FL)

**FNR-FL = % Non-FL biopsies that were histology Positive**

- **This is equivalent to 1-NPV**

# Positive Predictive Value (PPV)



## Comments

- In general, PPV is dependent on the prevalence of the disease condition in the study population:  
**High prevalences typically produce high PPVs**
- In these studies, PPV is assessed in conjunction with at least one additional complementary endpoint: FNR-FL

Although PPV is very high, there is a concern regarding FNR-FL, which is also high

# Three Definitions for PPV and FNR-FL



## Definition 1 : **Biopsy Level**

**BIOPSY PPV:** % of FL biopsies that are Histology Positive (HP)

**BIOPSY FNR-FL:** % of Non-FL biopsies that are HP

## Definition 2 : **Within-Subject Level**

For each subject, % of FL biopsies that are HP

**WSUB PPV:** Average across these “Within-Subject” percentages

For each subject, % of Non-fluorescent biopsies that are HP

**WSUB FNR-FL:** Average across these “Within-Subject” percentages

## Definition 3: **Subject-Level**

A subject has a score = 1 if **all** FL biopsies are HP

**SUB PPV:** Average across these scores

A subject has a score = 1 if **at least one** Non-FL biopsy is HP

**SUB FNR-FL:** Average across these scores

# Table 1: PPV/FNR-FL for all Studies



## STUDY ALS-3: PHASE 3 (170 Subjects)

(Median #Biopsies = 3 ; Median # Fluorescent Biopsies = 2 )

PPV			FNR-FL		
<b>BIOPSY (N=319)</b>	WSUB (N=165)	SUB (N=165)	<b>BIOPSY(N=160)</b>	WSUB (N=143)	SUB (N=143)
98%	98%	96%	81%	79%	80%

## STUDY ALS-28: PHASE 2 ( 33 Subjects)

(Median #Biopsies = 9 ; Median # Fluorescent Biopsies = 6 )

PPV			FNR-FL		
<b>BIOPSY (N=183)</b>	WSUB (N=33)	SUB (N=33)	<b>BIOPSY(N=112)</b>	WSUB (N=33)	SUB (N=33)
96%	96%	85%	76%	76%	94%

## STUDY ALS-30: PHASE 2 (36 Subjects)

(Median #Biopsies = 11; Median # Fluorescent Biopsies = 11 )

PPV			FNR-FL		
<b>BIOPSY (N=354)</b>	WSUB (N=33)	SUB (N=33)	<b>BIOPSY(N=16)</b>	WSUB (N*)	SUB (N*)
97%	97%	78%	81%	N/A	N/A



# FL Level vs Histology Cellularity

- The studies record fluorescence as none, weak and strong
- The studies record histology as cellularity percentages 0% to 100% (with 0% as negative histology)
- The next table refines Table 1 to reflect these levels

# Table 2: FL Level vs Histology Cellularity



STUDY ALS-3				
	HISTO = 0%	HISTO = [1-50%]	HISTO = [>50% ]	TOTAL
FL = NONE	30 (10%)	102 ( 64%)	28 (17%)	160
FL = WEAK	5 (3%)	55 (33%)	106 (64%)	166
FL = STRONG	2 (1%)	7 (5%)	144 (94%)	153
STUDY ALS-28				
	HISTO = 0%	HISTO = [1-50%]	HISTO = [>50% ]	
FL = NONE	27 (24%)	77 (69%)	8 (7%)	112
FL = WEAK	7 (8%)	60 (67%)	23 (25%)	90
FL = STRONG	0	10 (11%)	83 (89%)	93
STUDY ALS-30				
	HISTO = 0%	HISTO = [1-50%]	HISTO = [>50% ]	
FL = NONE	N/A	N/A	N/A	N/A
FL = WEAK	8 (4%)	39 (22%)	137 (74%)	184
FL = STRONG	3 (2%)	29 (18%)	129 (80%)	161
OVERALL FINDINGS				
	HISTO = 0%	HISTO = [1-50%]	HISTO = [>50% ]	
FL = NONE	57 (21%)	179 (66%)	36 (13%)	272
FL = WEAK	20 (5%)	154 (35%)	266 (60%)	440
FL = STRONG	5 (1%)	46 (11%)	356 (87%)	407

# FL Level vs Tumor Type

- Strong fluorescence corresponds to solid tumor
- Weak fluorescence corresponds to solid or infiltrative tumor
- Weak fluorescence is more likely in areas at the tumor margins
- However, in areas of non-fluorescence, tumor is also likely to be present (largely infiltrative)

NDA 208630

# EXPLORATORY ANALYSES

# Table 3: Study ALS-3 Data

## Fluorescence/Histology by Biopsy Region

### 5-ALA FL arm only

- Biopsy regions are Core, Margin, and Distant
- Fluorescence is:  
Strong (SF) ; Weak (WF) ; None (NF)
- Histology is either Positive (POS) or Negative (NEG)

	SF & POS	SF & NEG	WF & POS	WF & NEG	NF & POS	NF & NEG
CORE	114 (82%)	1	14	0	10	0
MARGIN	12	0	116 (83%)	4	7	0
DISTANT	0	0	2	0	108 (78%)	29



# Exploratory Analyses in Study ALS-3

Study ALS-3 included the endpoint:

- “Complete” resection = % patients whose Post-operative MRI was classified as tumor-free

This endpoint will be evaluated next for possible relationships to Fluorescence

# “Complete” Resection

## “Complete” resection rates in Study ALS-3:

- % in the 5 ALA arm is 64%
- % in the Control Arm (WL) is 38%.
- The difference is 26% [95% CI: (16%, 36%)]

# Fluorescence vs “Complete” Resection



## 5-ALA FL arm only

- The analysis of 5-ALA FL arm showed that the biopsies of the distant **non-fluorescent** tissue was histology positive for 4 out of 5 patients
- If it is assumed that
  - The non-FL tissue was not resected
  - The MRI enhances histology positive tissueThen % Complete Resections on histology positive patients should be less than % Complete Resections on histology negative patients
- Next table shows that the proportions are similar



# Fluorescence vs “Complete” Resection

## 5-ALA FL arm only



<b>**N = 137</b>	<b>Resection Status</b>	
	<b>Complete</b>	<b>Incomplete</b>
<b>Negative Histology ( n = 29 )</b>	12/29 (41%)	17/29 (59%)
<b>Positive Histology ( n = 106 )</b>	38/106 (36%)	68/106 (64%)

\*\*2 of 137 patients had missing MRI

# Observations on Exploratory Results

## Study ALS-3

- Complete Resection Rate for the 5-ALA Arm was greater than the Complete Resection Rate for the Control Arm
- For the 5-ALA Arm Alone
  - Fluorescence Level was determined by Biopsy site
  - Histology was largely Positive regardless of Biopsy site
  - Complete Resection Levels for patients whose Non-FL Tissue was histology Negative was about the same as the Complete Resection Levels for patients whose Non-FL tissue was histology Positive

NDA 208630

# CONCLUDING REMARKS

# Concluding Remarks



- PPV was very high, and the complementary biopsy-level FNR-FL also presented with high percentages (about 4 in 5 non-FL biopsies were histology positive)
- The intensity of FL correlates with tumor cellularity
- The 5-ALA FL Arm results did not provide for a direct link between PPV and Complete Resection

# Concluding Remarks



- **The added value of a new diagnostic**  
Its ability to correctly classify disease status of cases where standard diagnostics are uncertain
- **The diagnostic differential of fluorescence is not clear**  
From Study ALS-3 (5-ALA FL arm):  
Fluorescence can be predicted by biopsy region, and region corresponds more closely to histology than fluorescence
- **The added value of 5-ALA FL is more directly addressed by the increased “Complete Resection” in 5-ALA FL Arm versus Control WL Arm in Study ALS-3**  
This might be biased because of the absence of operator-blinding in study design

# BACK-UP SLIDES

# Patient Reported Outcomes



- **General Measure for Cancer Patients**
  - European Organization for Research and Treatment of Cancer QLQ-30 (EORTC)
  - Functional Assessment of Cancer Therapy (FACT)
- **Disease Specific**
  - EORTC BN-20
  - FACT-Br (Brain)

# Neurocognitive Function Assessments



- Controlled Oral word Association Test
- California Verbal Learning Test
- Grooved Pegboard Test
- Hopkins Verbal Learning Rest
- Mini-Mental State Exam
- Trail Making Test
- Weshler Adult Intelligence Scale
- Rey-Osterrieth Complex Figure Test



# Study Design in Glioma

- Randomize patients with glioma to either receive the drug 5-ALA or not in 10:1 ratio. Blind the surgical team (including the main surgeon) so they don't know if the patient got the drug. Surgical team would also be blinded to the randomization ratio. This controls the **operator bias**.
- The surgery would be done as completely as possible under standard conditions. Once deemed complete, they would open the randomization code and see whether they can shine the fluorescence or not. If there is fluorescence they could biopsy or resect.