FDA Briefing Document
Medical Imaging Drugs Advisory Committee Meeting
May 10, 2017

NDA 208630
5-ALA (5-aminolevulinic acid HCl)
Applicant: NX Development Corp.

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought (…5-aminoleuvulinic acid HCL..) to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

Glossary of Terms

5-ALA	5-aminolevulinic acid hydrochloride
AE	Adverse Event
BBB	Blood Brain Barrier
CSF	Cerebral Spinal Fluid
EOR	Extent of Resection
FL	Fluorescence Light
GBM	Glioblastoma Multiforme
HGG	High Grade Glioma
KPS	Karnofsky Performance Status
NIHSS	National Institutes of Health Stroke Scale
NPV	Negative Predictive Value
OS	Overall Survival
PFS	Progression Free Survival
PpIX	Protoporphyrin IX
PPV	Positive Predictive Value

Listing of Tables

1. Introduction

In December 2016, NXDC submitted a new drug application (NDA) for the following indication**:**

> *". . . imaging agent to facilitate the real time detection and visualization of malignant tissue during glioma surgery"*

This product has been approved in Europe since 2007 for the following indication:

> *5-ALA is indicated in adult patients for visualization of malignant tissue during surgery for malignant glioma (WHO grade III and IV).*

The drug, 5-ALA (5-aminolevulinic acid hydrochloride), is a natural metabolite in the human body that is produced with the hemoglobin metabolic pathway. Exogenous 5-ALA is orally administered, acts like a proagent, and has penetration of the blood-brain barrier (BBB) and tumor interface in brain tumors. Once 5-ALA is taken up by malignant glioma cells, it is metabolized into the fluorescent metabolite, protoporphyrin IX (PpIX). Possible mechanisms of selective accumulation of PpIX in neoplastic tissue include increased activity of PpIX producing enzyme porphobilinogen deaminase and/or a decreased activity of the PpIX converting enzyme ferrochelatase in tumor cells compared to normal cells. When excited by the appropriate wavelength, it emits fluorescence in the red wavelength. This can be detected with operating microscopes adapted to correspond to the appropriate excitation and emission wavelengths.

The recommended dose is 20 mg 5-ALA per kilogram body weight. The proposed label recommends caution with use in patients with renal or hepatic dysfunction. The safety and efficacy have not been tested in children and adolescents less than 18 years of age.

From a regulatory standpoint we have the following considerations:

i. This is an imaging drug belonging, based on its mechanism of action, to the pharmacological class of optical agents. The Imaging Drugs Guidances of 2004 do not specifically refer to optical agents but we believe the main concepts expressed in the Guidances apply here as well. The concepts are of clinical utility and performance. The utility can be obvious on its face and well accepted and, if it is not, it has to be demonstrated in a clinical investigation. If clinical utility is already well-established then demonstrating the drug's performance would be sufficient. The efficacy claims of imaging agents can be based on such endpoints as structural delineation (lesion visualization), functional measurement (ejection fraction), diagnostic accuracy (sensitivity and specificity of detecting disease or pathology), and change in patient management. Performance of an imaging agent has to be compared to a truth standard (histopathology) or a clinically meaningful comparator (contrast to non-contrast).

ii. Our drug regulations require that safety and effectiveness of a drug are established on the basis of adequate and well controlled clinical investigations (usually more than one).

iii. The data obtained in such investigations may and may not be owned by the applicant. The latter is the so called "505 b 2" pathway used in the case of the current application.

2. Background

Malignant gliomas account for the majority of newly diagnosed primary brain cancers in adults each year. Approximately 14,000 cases are found each year. Although not as common as breast or lung cancer, gliomas are associated with a disproportionately higher morbidity and mortality. An estimated 17,000 deaths will be attributed to primary malignant brain and other CNS tumors in the US in 2017[1]. The age-adjusted incidence of glioblastoma ranges from 4.7 to 5.7 per 100,000.

Primary gliomas arise de novo while secondary gliomas arise from low grade tumors such as astrocytomas or oligodendrogliomas. The median age is 64 years although the secondary tumors usually occur 10-15 years younger. Risk factors include a history of ionizing radiation, history of neurofibromatosis types 1 and 2, Li-Fraumeni and Lynch syndromes while a history of allergic/atopic conditions (i.e. asthma, hay fever, eczema) may reduce the glioma risk by about 40%.

Malignant gliomas are histologically heterogeneous and invasive arising from glial cells. They are infiltrative in nature and resection will require removal of tumor and involved brain tissue. They have been classified by the WHO into four prognostic categories based on histologic appearance. Grades 3 and 4 are considered high-grade and are the most rapidly growing tumors. In 2016, WHO released a new classification scheme that incorporates the growing understanding of molecular pathogenesis to stratify patients for treatment after surgical resection.

The natural history of this disease when left untreated is a life expectancy of 6 months from diagnosis. With the addition of surgery and whole brain radiation, survival has been extended to 12-14 months. The average life expectancy of a patient above 60 years of age is one year. There have been only small incremental improvements in survival with the addition of chemotherapeutic and biologic agents to the treatment strategy.

Patients with high-grade gliomas usually present with neurologic manifestations that can be subacute and are dependent on the location of the tumor in the brain. The onset can mimic other primary brain tumors and metastatic disease. The most common manifestations include headache and seizures while other neurologic findings are present in about 20% and reflect the tumor location near eloquent structures affecting vision, language and motor function.

[1] CBTRUS Fact sheet 2016

Association Between the Extent of Tumor Resection (EOR) and Patient Survival

It is generally accepted in clinical practice that extent of tumor resection, age at diagnosis and Karnofsky performance status are prognostic factors for survival, but survival will vary with tumor grade. Overall survival in GBM is poor with the range of patients surviving 5-years from 0.005% to 4.7%. Despite significant clinical advances and an improvement in our understanding of molecular biology, the overall survival remains the same.

Although maximal safe surgical resection is the standard of care for gliomas, there are no randomized controlled studies providing evidence that it is better than debulking. The need to balance maximum cytoreduction with preservation of healthy brain tissue is challenging due to the infiltrative nature of these tumors. Evidence to support the concept of maximal safe resection comes from retrospective, observational studies only. The determination of resectability will depend on tumor morphology, tumor location and prognostic factors such as age and Karnofsky performance status while tumor size and location may influence survival. Surgical intervention can reduce the mass effect, reduce the need for high dose steroids and provide a tissue diagnosis. When the disease recurs, the recurrence is locally within 2cm of the previously resected margin.

To the best of our knowledge there have been no prospective randomized controlled clinical studies demonstrating that extent of resection improves survival. Most of the studies are retrospective reviews and rely on imaging to define progression of disease. However, many authors have demonstrated an impact on overall survival if there is a complete resection, as defined by MRI in the immediate post-operative period. Gross total resection is rarely possible because of anatomic or technical factors. The surgeon's ability to determine the resectability on pre-operative imaging frequently does not correlate with the intraoperative findings. Albert, et al.[2] compared the presence of residual enhancement on post-operative MRI to the surgeon's assessment of residual tumor. They found that MRI revealed areas of residual enhancement consistent with tumor three times more often than predicted by the surgeon. Using the radiologic response as a primary endpoint has merit as it is a direct measure of therapeutic effect not affected by the natural history of the disease however the ability of the radiologic response to consistently predict meaningful clinical benefit is variable.

The study by Lacroix[3] et al. evaluated pre- and post-operative MRIs of 416 patients who underwent surgical resection to assess residual tumor volume and extent of resection. Resection of 98% of the tumor volume was associated with a survival advantage of 13 months compared to 8 months. In a retrospective analysis of 500 consecutive patients, Sanai[4] et al. evaluated 3D tumor volume reconstructions and compared the pre- and

[2] Albert, et al. "Early post-operative MRI after resection of malignant glioma: objective evaluation of residual tumor and its influence on regrowth and prognosis" *Neurosur*g 1994; 34(1):45-61

[3] Lacroix, et al. "A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent or resection, and survival" *J Neurosurg* 2001; 95:190-198

[4] Sanai, et al. "Glioma extent of resection and its impact on patient outcome" *Neurosurg* 2008; 62(4):753-766

post-operative images, interpreted by readers blinded to outcome, and reported that aggressive resection was associated with improved overall survival. The authors concluded that a 78% reduction or greater in tumor volume was associated with prolongation of survival. Aldave[5] et al. in a retrospective analysis of 52 patients reported that completeness of tumor resection, as determined by post-operative MRI, was associated with improvement in overall survival. A retrospective review of 1229 consecutive patients by Li et al.[6] found that if there was a complete tumor resection the overall survival was 15.2 months compared to 9.8 months with residual disease. This numerical difference remained even when adjusted for such variables as age, KPS, pre-operative symptoms, and enhancement.

Additional support favoring a relationship between EOR and survival comes from a retrospective review of forty six patients by Orringer et al.[7] showing there was a 1-year survival advantage when the EOR exceeded 90% defined as the absence of tumor on post-operative MRI. The location of the tumor and the ability of the surgeon to determine residual disease intra-operatively influence the EOR. Determining tumor response to adjuvant therapy is also assessed using MRI. The use of imaging to assess post-operative residual tumor status and (completeness of resection) and tumor recurrence is the standard of care in the management of neuro-oncological disease.

The association between increasing the EOR and the residual volume (RV) detected was studied by Chaichana et al[8,9]. In a retrospective review of 292 patients with newly diagnosed glioblastoma, they found that the EOR and RV were associated with survival. An EOR of 70% and a RV of 5cm^3 were the proposed thresholds to achieve surgically.

<u>Progression Free Survival (PFS) as an Efficacy Endpoint in Glioblatoma: Relationship to Overall Survival (OS)</u>

Overall survival is considered the definitive primary endpoint for studies of therapeutics in patients with newly diagnosed or recurrent disease. A drawback of using OS is that it could potentially be influenced by life-prolonging subsequent therapy administered after patients leave the study (typically upon progression).

PFS can directly measure the efficacy of initial therapy, unaffected by treatment at progression and study results can be obtained sooner. The challenges with PFS for this population are the pitfalls associated with the use of clinical and imaging criteria.

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[5] Aldave, et al. "Prognostic value of residual fluorescent tissue in glioblastoma patients after gross total resection in 5-ALA guided surgery" *Neurosurg* 2013; 72(6):915-92

[6] Yan, et al. "The Influence of maximum safe resection of glioblastoma on survival in 1229 patients: Can we do better than gross-total resection?" *J Neurosurg* 2016; 124:977-988

[7] Orringer, et al. "Extent of resection in patients with glioblastoma: limiting factors, perception of resectability and effect on survival" *J Neurosurg* 2012; 117:851-859

[8] Chaichana, et al. "Establishing percent resection and residual volume thresholds affecting survival and recurrence for patients with newly diagnosed intracranial glioblastoma" *Neuro-Oncolgy* 2014; 16(1):113-122

[9] Chaichana, et al. "When gross total resection of a glioblastoma is possible, how much resection should be achieved?" *World Neurosurg* 2014; 82(1/2):E257-265

In clinical trials of patients with gliobalstoma, the common endpoints are PFS at 6 months and OS at 12 months. Ballman et al.[10], evaluated these endpoints from eleven pooled NCCTG trials and found the PFS at 6 months and OS at 12 months were 43% and 41%, respectively, for patients with newly diagnosed disease and 9% and 14% for patients with recurrent disease. They concluded that there was a strong association between PFS and OS.

Neidert et al[11] showed that median OS in 76 glioblastoma patients after gross total resection was 20.4 months (95 % confidence interval (CI) 18.5–29.0). A similar effect was found for PFS.

A meta-analysis based on 91 clinical studies by Han et al.[12] using linear regression analysis to evaluate the correlation between median PFS and median OS, as well as the hazards ratio in PFS and OS, found a good correlation between PFS and OS and the slope of the curve did not change if response assessment in neurooncology (RANO) criteria or Macdonald criteria were used. A 10% risk reduction for PFS was associated with an 8% risk reduction in OS. The results appear to support the value of PFS for assessment of response to treatment.

The study of therapies in patients with high grade glioma would benefit from the development of end points that rely on novel imaging approaches, as well as measures of patient function and well-being. There is little experience with evaluation of patient reported outcomes or quality of life. A Cochrane report[13] in 2014 found this to be a weakness of the published literature.

3. Study Design

The Applicant has provided 5 clinical trials to support the safety and efficacy of the product. Out of these studies, ALS-28, ALS-30, and ALS-3 provide data to support the efficacy of the study drug. (The remaining studies are included as part of the safety analysis.) Only one study, ALS-3, is a phase 3 radomized controlled study.

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[10]Ballman, et al. "The relationship between six-month progression-free survival and 12-month overall survival end points for phase II trials in patients with glioblastoma multiforme" *Neuro-Oncology* 2007; 9(1): 29-38.

[11]Neidert, et al. "The influence of intraoperative resection control modalities on survival following gross total resection of glioblastoma*", Neurosurg Rev* 2016; 399-401.

[12] Han, et al. "Progression-free survival as a surrogate endpoint for overall survival in glioblastoma: a literature-based meta-analysis from 91 trials" *Neuro-Oncology* 2014; 16(5): 696-706.

[13] Barone, et al. "Image guided surgery for the resection of brain tumors (review)" Cochrane Database of Systematic Reviews 2014, Issue 1. Art. No.: CD009685 www.cochranelibrary.com

The applicant, on a post hoc basis, has selected the biopsy-level PPV, originally a secondary endpoint, to demonstrate efficacy in all three trials.

Table 1 Summary of Studies Evaluated for Safety and Efficacy

Study	Description	Design	Duration	No of Patients
ALS.8	Phase 2 Study of 5-ALA for fluorescence guided resection of malignant gliomas	Randomized, double-blind, three dose levels (Safety and pK)	4 weeks post operation	N=21
ALS.28	Phase 2 Study of 5-ALA for fluorescence guided resection of primary malignant gliomas	Single arm, uncontrolled	4 weeks post operation	N=36
ALS.30	Phase 2 Study of 5-ALA for fluorescence-guided resection of recurrent malignant gliomas	Single arm, uncontrolled	6 months post operation	N=40
ALS.3	Fluorescence-guided resection of malignant gliomas with 5-ALA vs. conventional resection	Parallel arm, randomized, reader-blinded, test versus conventional resection	Up to 18 months post operation	Drug N=201 Control N=206
ALS.32	Study of the fluorescence-guided resection of malignant gliomas using 5-aminolevulinic acid	Single arm, uncontrolled (Safety)	Until death or not more than 6 weeks after last patient enrolled	N=243

The Inclusion/Exclusion Criteria were similar across all studies. Pre-operative MRI showing an enhancing lesion with a determination of resectability were the main criteria. For the efficacy analysis, the final histology had to be consistent with WHO Grade 3 or 4 classification. ALS-30 specifically addressed the use of the drug in the setting of surgical resection for recurrent disease, while ALS-28 included only primary resections. ALS-3 included some patients with prior surgery (these were considered protocol deviations).

All studies used the same assessment tools which included MRI, Karnofsky Performance Status (KPS), and NIH Stroke Scale (NIHSS). The patients underwent pre-operative MRI to deterimine eligibility and resectability, a post-operative MRI within 48 hours, and then every 3 months. KPS and NIHSS were assessed at baseline, immediate post-operative, 7 days, 4-6 weeks, and each subsequent visit.

Patients in all the studies then received chemotherapy with temozolomide post surgery. Not all patients completed the expected adjuvant therapies. All patients also received 4 mg dexamethasone three times a day for at least 2 days before surgery and continued until early MRI (72 hrs post-op).

ALS-28

This was a prospective, multi-center, single arm, uncontrolled study to assess the reliability of fluorescence to identify tumor in 33 patients with primary GBM. All patients received the study drug. After debulking, three biopsies were taken from areas of "weak", "strong" and non-fluorescing areas. These were defined as pink, red or blue areas. To complement the surgeon's assessment of the intensity of fluorescence, the fluorescence intensity was confirmed by spectrophotometric measurements. The areas of non-fluorescence at the tumor margin and in cortex distant to tumor were measured spectroscopically as well and biopsied if safe. The biopsies were examined by the central pathology lab for their tumor cell content (5 point range: 0%, 1-25%, 26-50%, 51-75%, 76-100%) and histological differentiation (vital, solid, proliferating tumor; infiltrative tumor; necrosis; normal tissue).

In addition, the completeness of resection was verified by lack of enhancement on post-operative MRI.

Patient Disposition

- Enrolled: n=39, 36 patients received the drug, 33 patients eligible for Full-Set Analysis
- Withdrawn: n=8
- Protocol Deviations:
    - Steroids not given per protocol was the most common
    - Follow-up assessments missed or not done
- 6 were excluded from the Full-Set Analysis
    - 3 did not meet entry criteria
    - 2 did not meet histology criteria
    - 1 did not have surgery

Endpoints

Primary

- Positive predictive value of tissue fluorescence, defined as the percentage of patients showing positive tumor cell identification in all biopsies taken from sites with weak and strong fluorescence. (A biopsy was termed as "positive tumor cell identification" if the central pathology lab observed a tumor cell content greater than 0%).

Secondary

- Positive predictive value of tissue fluorescence at the biopsy level
- Evaluation of the quality of fluorescent and of non-fluorescent tissue adjacent to fluorescent tissue areas and tumor distant cortex observed by the surgeon with respect to:
    - fluorescence intensity measured spectrometrically
    - tumor cell quantity
    - histological differentiation (vital, solid, proliferating tumor; infiltrative tumor; necrosis; normal tissue)
- Assessment of the location of residual fluorescence observed intraoperatively (infiltration of eloquent structures) by neuronavigation and comparison with contrast enhancement (residual tumor) on early postoperative MRI
- Evaluation of the simplification of resection using fluorescence-guided resection (through a surgeon questionnaire)
- Determination of safety of 5-ALA

ALS-30

This was a single arm, multi-center, uncontrolled study to assess reliability of fluorescence to identify tumor in 36 patients with recurrent GBM. After resection, the tumor bed was examined under conventional (white) light to delineate areas of abnormal and normal tissue for biopsy. The same areas were examined under blue light and classified as weak, strong or non-fluorescent.

Patient Disposition

- Enrolled: n=40 (part of safety analysis), n=4 excluded (final path exclusion, no prior surgery, faulty microscope)
- Efficacy: n=36 in Full-Analysis-Set
- Withdrawn: n=1 lost to follow-up
- Protocol Deviations :
    - 29 had evaluations outside visit schedule
    - 15 violated the time from administration to surgery
    - 10 did not receive dexamethasone as planned

Endpoints

Primary

- Determine the positive predictive value of tissue fluorescence at the patient level using the definition of PPV as in the other studies

Secondary

- Calculation of PPV at the biopsy level
- % patients without residual disease
- Overall survival
- Observation of changes in KPS and NIH scale

ALS-3

This was the only randomized, reader-blinded, controlled, multi-center study using 5-ALA to resect malignant gliomas, with central neuro-pathological and neuro-radiological assessment blinded to treatment arm. Biopsy methodology was not clearly defined and surgeons were directed to take biopsies of the tumor core, margin and normal adjacent areas and note the corresponding fluorescence. Additional biopsies could be taken at the surgeon's discretion.

At the time this study was done, surgery using other potential techniques for optimizing resection, such as intra-operative MRI, ultrasound or neuronavigation were not considered the proper comparators, since none of these techniques had been validated in terms of specificity, sensitivity, patient benefit or safety and back then were not uniformly used in the neurosurgical community.

Patient Disposition

- Enrolled: n=415
- Withdrawals: n=66, most due to final histology inconsistent with protocol
- Protocol Deviations: n=331, most due to failure to record NIH stroke scale (n=151) or the follow-up MRI not done or out of time window (n=129)

Endpoints

Primary

- Completeness of resection on post-op MRI
- Progression free survival at 6 months

A hierarchical approach was used wherein each primary efficacy criterion could be tested on the nominal two-sided significance level of 5% to maintain the multiple type I error of 5%. If the first primary endpoint showed significance, the second primary endpoint would be subjected to confirmatory statistical testing.

Secondary

- Absolute volume of residual tumor
- Relative reduction of tumor volume
- Overall Survival
- Time to event Analyses
    - Neurologic status at 6 mos.
    - Time to tumor progression on MRI
    - Time to re-intervention
    - Time to re-operation

4. Efficacy

All three studies, for the purposes of the currently submitted NDA, base the efficacy claim on what the Applicant calls biopsy level PPV. Regardless of the original endpoints in the studies, all the efficacy data has been presented as PPV. In addition, the Applicant has supported this approach by re-analyzing twelve published studies to obtain the PPV for each.

PPV

For the purposes of this NDA the Applicant has defined this value at the lesion/biopsy level. We have considered this as well as two other ways to define PPV:

- At the biopsy level: the percentage of histology positive fluorescent biopsies among all fluorescent biopsies.
- At the Within-Subject level: The average across patients of each patient's PPV, where the patient's PPV is the percentage of histology positive fluorescent biopsies among all fluorescent biopsies for that patient.
- At the patient level: The percentage of patients for each of whom all fluorescent biopsies are histology positive.

To gain additional insight into the performance of the study drug since there were a considerable number of biopsied non-FL sites, the histology outcomes for the tissue taken from such sites provide for a statistic complementary to PPV. That complementary statistic is called NPV and that also is defined in the following three ways:

- At the biopsy level: the percentage of histology negative biopsies among all non-fluorescent biopsies.
- At the Within-Subject level: The average across patients of each patient's NPV, where the patient's NPV is the percentage of histology negative biopsies among all non-fluorescent biopsies for that patient.
- At the patient level: The percentage of patients for each of whom all non-fluorescent biopsies are histology negative.

The following table shows the PPV and the calculated NPV for each trial.

Table 2 PPV/NPV All Three Studies

STUDY ALS-3 PHASE 3 (170 Subjects) (Median # Biopsies = 3; Median # Fluorescent Biopsies = 2)						
PPV				NPV		
BIOPSY (N=319)	W-SUB (N=165)	SUB (N=165)		BIOPSY (N=160)	W-SUB (N=143)	SUB (N=143)
98%	98%	96%		19%	21%	20%
STUDY ALS-28 PHASE 2 (33 Subjects) (Median # Biopsies = 9; Median # Fluorescent Biopsies = 6)						
PPV				NPV		
BIOPSY (N=183)	W-SUB (N=33)	SUB (N=33)		BIOPSY (N=112)	W-SUB (N=33)	SUB (N=33)
96%	96%	85%		24%	24%	6%
STUDY ALS-30 PHASE 2 (36 Subjects) (Median #Biopsies = 11; Median # Fluorescent Biopsies = 11)						
PPV				NPV		
BIOPSY (N=354)	W-SUB (N=33)	SUB (N=33)		BIOPSY (N=16)	W-SUB (N*)	SUB (N*)
97%	97%	78%		19%	N/A	N/A

*N is too small for meaningful calculations

PPV and NPV for a particular condition are dependent on the prevalence of the condition in the study population. In addition, PPV as a stand-alone primary endpoint needs to be assessed in conjunction with at least one additional "detection" endpoint, such as NPV, or possible clinical benefit. Although un-controlled, the data presented above are consistent with the high PPV regardless of the level at which it has been determined. Of concern is the corresponding NPV, where it could be obtained, which is quite low.

Another way to analyze the data is to compare the surgeon's assessment of the intensity of fluorescence to the histology. In these studies the surgeon was typically directed to biopsy areas of "strong", "weak", and no fluorescence when feasible. If we define cellularity as no cells, low (comprising up to 50% of the biopsy) and high (comprising >50%) we can correlate the two parameters to provide some insight into how well the drug could predict presence of tumor.

Table 3 Fluorescence Level versus Histology Cellularity Level

STUDY ALS-3				
	HISTO = NEG	HISTO = LOW	HISTO = HIGH	TOTAL
FL = NONE	30 (19%)	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 = NEG	HISTO = LOW	HISTO = HIGH	
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 = NEG	HISTO = LOW	HISTO = HIGH	
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
ALL STUDIES COMBINED				
	HISTO = NEG	HISTO = LOW	HISTO = HIGH	
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

While the areas of fluorescence correspond to solid tumor or infiltrative cells, if the area is not fluorescent, tumor is likely to be present as well. The correlation between strongly fluorescent areas and solid tumor is very high but less so in those areas at the margins where the pattern is more infiltrative. The importance of this comes into play as those areas of ambiguity or normal appearing tissue, as seen under standard operating light also contain tumor cells even if they are non-fluorescent. When fluorescent tissue is not resected the post-operative MRI may or may not show residual tumor contrast enhancement but, even without residual fluorescence, tumor may be present.

Review of the literature reveals several publications which address the accuracy of 5-ALA by reporting other measures such as sensitivity, specificity and NPV. The challenge remains in obtaining tissue from areas of normal brain. The following summarizes the data available from the literature review:

Table 4 Summary of Literature for 5-ALA

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
Yamada et al (2015)	97	95	53	92	69
Hauser et al (2016)	12	81	43	96	12.5
Stummer et al	9	85	100		
Diez Valle et al (2011)	36	91	89	100 (S) 97 (W)	66
Hefti et al (2008)	57	100 (S) 76 (W)	98(S) 85(W)		
Zhao et al (2015)	Meta-analysis	87	89		

S=strongly fluorescent; W=weakly florescent

Although the sensitivity and PPV of 5-ALA are acceptable, the lower specificity and NPV are concerning. If there is fluorescence there will be tumor but the converse is not necessarily true.

The following tables show analysis of studies ALS-3 and ALS-30 to evaluate the performance between white light (WL) and fluorescent light (FL), where WL positive means abnormal under the white light and WL negative means normal under the white light. The data for ALS-3 are presented in Table 5:

Table 5 ALS-3 Biopsy-Level Data

	Histology Positive (n=442)			Histology Negative (n=37)	
	FL Positive	FL Negative		FL Positive	FL Negative
White Light Positive	310	21	White Light Positive	7	0
White Light Negative	2	109	White Light Negative	0	30

In Study ALS-3 (phase 3 study), these biopsy-level data show the following performance along with prevalence of 92% for malignant tissue.

Table 6 ALS-3 Calculated Performance

	Sensitivity	Specificity	PPV	NPV
Fluorescence Light	71%	81%	98%	19%
White Light	75%	81%	98%	21%

The data for ALS-30 are presented in Table 7:

Table 7 ALS-30 Biopsy-Level Data

	Histology Positive (n=355)			Histology Negative (n=15)	
	FL Positive	FL Negative		FL Positive	FL Negative
White Light Positive	196	0	White Light Positive	1	0
White Light Negative	146	13	White Light Negative	11	3

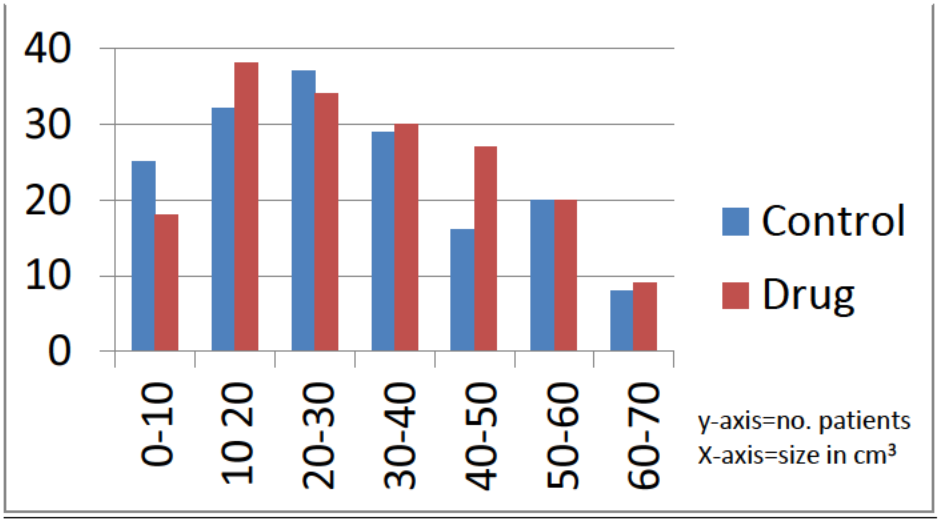
In Study ALS-30 (a phase 2 study performed subsequent to ALS-3), these biopsy-level data show the following results along with prevalence of 96% for malignant tissue.

Table 8 ALS-30 Calculated Performance

	Sensitivity	Specificity	PPV	NPV
Fluorescence Light	96%	20%	97%	19%
White Light	55%	93%	99%	8%

Completeness of Resection (Extent of Resection (EOR))
The first primary endpoint in ALS-3 was the completeness of resection as assessed on an immediate post-operative MRI. The ability to achieve a complete resection is determined by many factors such as size and the location away from eloquent areas of the brain, independent of tumor visualization.

Table 9 Tumor Volume by Study Arm



The study arms were similar in the distribution of pre-operative tumor volume. When looking at the residual volume for the Full-Analysis-Set, median volume of residual tumor for patients in the FL-group was 0.0 cm^3 versus 0.5 cm^3 in patients in the WL-group.

Table 10 Localization of Tumors from Available Data from ALS-3 Study

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

There are slightly more tumors in or near eloquent areas of the brain in the FL study arm.

The results for completeness of resection are compared between the arms in Table 11:

Table 11 Patients without Residual Contrast Enhancement on Post-Op MRI (Study ALS-3)

	5-ALA (n=139)	White Light (n=131)	Odds Ratio (95%CI)
All Patients	90 (65%)	47 (36%)	3.28 (1.99-5.40)

Fluorescence versus Complete Resection Correlations (additional analyses)
In the controlled study (ALS-3), there were generally three biopsies/patient, with one of these non-fluorescent. The table below presents cross tabulations of the histology for the non-fluorescent biopsy with early post-surgery MRI status for patients.

Table 12 Fluorescence versus Complete Resection Correlations

	Total MRIs N	MRIs with Complete Resection n	Percentage
Non FL Biopsy is Histology Negative	**138**	**48**	**35%**
Non FL Biopsy is Histology Positive	**29**	**12**	**41%**

If it is assumed that the tissue around the non-FL biopsy was not resected, but reflected the histology result for the biopsy, then the expectation would be that the percentage of patients with Complete Resection among patients who were Histology Negative for the Non-FL biopsy would be greater than the percentage of patients with Complete Resection among patients who were Histology Positive for the Non-FL biopsy. The table above shows that the results are similar.

Overall Survival
A greater debulking/resection would be expected to lead to better survival, a clinical benefit if the drug allows resection of more tissue.

Table 13 Survival (ALS-3)

	Median survival (months)
ALS-3	14.3 treated 13.7 control

However, the results of ALS-3 show no overall survival benefit in the treatment arm, Estimates of overall survival might have been influenced by re-interventions after study surgery.

Progression Free Survival
This was the second primary endpoint in ALS-3. At 6 months post-surgery, there is an apparent improvement in PFS in the 5-ALA arm based on the landmark 6-month analysis. At 6-months the proportion of patients is 11% in control arm and 21 % in the 5-ALA arm (FDA review is ongoing).

5. Safety

Studies ALS-8, ALS-28, ALS-30, ALS-3, and ALS-32 provide the safety data base used for analysis. In addition, the Applicant has provided the most recent PSUR (periodic safety update) submitted to the European Medicines Agency (dated 2015).

In these trials, patients received a single oral dose of 20mg/kg of 5-ALA 3-4 hours prior to surgery. Adverse events were collected throughout the immediate post-operative period and at each follow up visit.

Summary of Adverse Events

The severity and frequency of procedure-specific neurologic events depend on the site of the tumor and the degree of resection of tumor in or near eloquent areas of the brain.

Table 14 Summary of Adverse Events

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

Deaths

All deaths were not directly attributable to the study drug but rather to complications of anesthesia, nature of the surgical procedure and progression of disease. The most common events were thromboembolic such as pulmonary embolus or cerebral infarction. Cardiac issues contributed as well.

Other Serious Adverse Events

Of the 1,185 adverse events listed only 25 were attributed as related to the study drug. Five were categorized as serious events and included one each of the following: chills, exanthema generalized, respiratory insufficiency, hypertension, and hypotension. There were no discontinuations due to toxicity (Grade 1 to 4).

The other adverse events were considered mild to moderate and included transient elevation of liver function tests, photosensitivity and solar dermatitis. The remainder of the adverse events was attributed as unrelated to the study drug and was procedure related or disease related.

Neurologic Adverse Events

Of particular concern with the use of this drug is the potential for increased or worsening neurologic deficits post-operatively as a result of resection of more malignant tissue. In the only controlled study there were no significant differences in the two arms except for those events coded to vison. Below is a summary of the major neurologic events in each trial.

Table 15 Summary of Common Neurologic Events for all Studies

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		1			11	6
Aphasia	22	7	7	19	24	12
Dysarthria/Speech	1	3		3	15	15
Hygroma				3	1	1
Hemorrhage	1	1		3	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		2		3	1	
Cerebral Edema				2	0	3
Somnolence/Confusion		3			4	3
Hydrocephalus		1			1	2
Dizziness		2			1	4
Headache	5	4		8	12	11
Totals	**45**	**40**	**24**	**103**	**165**	**116**

The ALS-3 study showed that within the first 48 hours, 26% of patients with fluorescence guided resection deteriorated one to three points on the NIHSS, compared with 14.5% of the white light group. This deterioration was not sufficient to be detected by the KPS, and there were no significant differences in NIHSS or KPS between patient groups after 7 days, 6 weeks or 6 months.

Additional Safety Information

The Applicant provided an analysis of adverse events in study ALS-3 including neurologic status by time of onset. "Neurologically worse" was defined as a deterioration in the NIHSS by at least 1 point relative to the preceding visit. The proportion of event-free patients in the treatment was higher compared to the control arm (46% vs. 29% respectively). In addition, when "neurologically worse" was defined as a deterioration in the NIHSS by at least 2 points relative to the preceding visit, the proportions of event-free patients was higher in the treatment arm.

A retrospective report from 2015 (Honorate-Cia[14]) evaluated the safety profile of 5-ALA compared to historical controls whose surgery were not done with 5-ALA. The most notable observations were a longer operating time for the 5-ALA group.

A retrospective review by Chung and Elijamel[15] evaluated risk factors for elevated liver enzymes or hypotension. The authors reported that changes in liver enzymes were transient and mild and that hypotension was more likely if patients were on antihypertensive medications pre-operatively.

The Applicant provided a summary of their pharmacovigilance data. No actions were taken or initiated by any regulatory authority for safety reasons since marketing authorization has been granted. The estimated cumulative number of patients who have received the drug was 58,413.

Only two cases of accidental 5-ALA overdose were reported resulting in mild redness of the face. The adverse reactions more frequently reported with the drug include hypotension, elevation of LFT's, changes in blood values. Other events reported are procedure-specific rather than drug related.

The applicant recommends a training program for neurosurgeons prior to using the drug. This training provides information on techniques to optimize the use of 5-ALA fluorescence guided surgery (FGS).

[14] Honorato-Cia, et al. "Safety Profile of 5-ALA as a surgical adjunct in clinical practice: A review of 207 cases from 2008-2013" *J Neurosurg Anesthesiol* 2015; 27(4):304-309

[15] Chung, et al. "Risk factors for developing oral 5-ALA induced side effects in patient undergoing fluorescent guided resection" *Photodiagn Photodyn Ther* 2013; 10:362-367

6. Summary Findings from the Applicant's Studies and Supporting Literature

- There are no adequate and well controlled studies among the submitted scientific publications.
- The definitions of variables and endpoints assessed varied among the available reports.
- The Applicant's studies generally provide insufficient control of ascertainment bias for example in tissue sampling for histopathology verification of tumor status.
- There is general literature support for the notion that achievement of maximal safe tumor resection is associated with improved clinical outcomes such as survival.
- In the absence of curative surgical intent it is difficult to objectively define optimal tumor resection.
- Assessment of completeness of resection by amount of residual contrast enhancement in postoperative MRI shows an improvement in 5-ALA arm. However, MRI assessments have limitations and analysis of cross correlation between extent of resection and fluorescence is not supportive.
- There is insufficient evidence that 5-ALA enhances clinical outcomes such as survival or patient reported outcomes.
- There is reasonable concordance between positive levels of 5-ALA fluorescence and presence or degree of infiltration of tumor by histopathology.
- There is poor concordance between negative fluorescence and presence of tumor by histopathology.
- The added value of fluorescence compared to standard visualization as an aid in tumor resection could not be ascertained due to uncontrolled nature of the Applicant's studies.
- The safety profile of 5-ALA is generally acceptable for its proposed clinical use.

7. Draft Points for Consideration by the Medical Imaging Drugs Advisory Committee

Point 1

Please consider the efficacy outcomes used in this drug development program and their acceptability for substantiating the proposed claim.

a) Performance of imaging drugs is frequently assessed by comparing it to a certain Standard of Truth and measuring such parameters as sensitivity, specificity as well as positive and negative predictive value. Please discuss whether any of these efficacy measurements are applicable to this drug and its proposed use.

b) The Applicant has presented data from two Phase 2 studies and one Phase III study demonstrating the intraoperative detection of malignant tissue with the calculation of the proportion of such detections verified by histopathology. Please discuss the clinical significance of the observed rate of malignant tissue detection with the use of 5-ALA and whether the provided data on malignant tissue detection are sufficient for establishing efficacy of 5-ALA. Please discuss the potential clinical importance of "failed detection" rate, i.e. the proportion of histopathology positive tissue samples which did not fluoresce.

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.

d) The Applicant failed to demonstrate an improvement in overall survival by using 5-ALA to facilitate the intraoperative detection of malignant tissue during glioma surgery. Please comment on clinical significance, if any, of the observed improvement in progression free survival and of the lack of improvement in overall survival. Should either one be mentioned in the prescribing information if 5-ALA is approved for marketing in the US? Please discuss 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 in this setting.

Point 2

Please discuss possible risks associated with increased resection, e.g. potential for increased neurological deficits. Please discuss any other safety concerns you might have about this drug.

Point 3

Do you recommend the approval of 5-ALA for marketing in the US? If you recommend approval you may provide comments, if any, on the proposed indication statement.

Point 4

Please discuss potential clinical use of 5-ALA in the US and its interaction with other clinical modalities used in the care of patients with glioma. Please comment on the proposed training program and on a potential need to assess patient reported outcomes in the post-marketing setting.