CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208630Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	208630
Priority or Standard	Fast Type Designation
Submit Date(s)	12/6/2016
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Division/Office	DMIP/OND IV
Reviewer Name(s)	Betsy Ballard, MD
Review Completion Date	5/15/2017
Established Name	Gliolan (5-Aminolevulinic Acid)
(Proposed) Trade Name	Gleolan
Applicant	NX Development Corp
Formulation(s)	Oral powder
Dosing Regimen	20mg/kg given a single time 3-4 hours prior to surgery
Applicant Proposed Indication(s)/Population(s)	An imaging agent to facilitate the real time detection and visualization of malignant tissue during glioma surgery.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	*An imagining agent indicated as an adjunct to other neurosurgical tools, to visualize WHO grades III and IV gliomas intra-operatively during glioma surgery.* (This is the reviewer's proposed statement and may differ from the indication that will be approved)
Review Team	Clinical Reviewer: BALLARD, BETSY Statistician: MUCCI, ANTHONY Clinical Pharmacology: JOHN, CHRISTY S. Non-Clinical Reviewer: HONCHEL, RONALD Product Quality Reviewer: AMARTEY, JOHN K. Product Quality Reviewer: HABER, MARTIN T. Product Quality Microbiology Reviewer: PFEILER, ERIKA A. CDRH Consultants: OGDEN, NEIL and CHEN, COLIN KEJING (DSD/GSDB I) Regulatory Project Manager: SKARUPA, LISA M

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Glossary

5-ALA	5-aminolevulinic acid
AC	advisory committee
AE	adverse event
ALT	alanine aminotransferase
BBB	blood brain barrier
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	case report form
CSR	clinical study report
DMC	data monitoring committee
EANO	European Association of Neuro-Oncology
ECG	electrocardiogram
eCTD	electronic common technical document
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FN	False Negative
FNR-FL	False Negative Rate-Fluorescent
GCP	good clinical practice
GGT	gamma-glutamyl transferase
GRMP	good review management practice
ICH	International Conference on Harmonization
iMRI	Intra-operative MRI
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
LFT's	liver function tests
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat

NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NPV	negative predictive value
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PpIX	protoporphyrin IX
PPV	positive predictive value
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

The applicant has proposed the use of Gleolan (5-ALA) as an imaging agent to facilitate the real time detection and visualization of malignant tissue during glioma surgery. The recommended dose is a single oral dose of 5-ALA at 20mg/kg given 3 hours prior to surgery. It is not considered an NME, as 5-ALA in other forms, has been approved for several indications.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The application contains sufficient evidence based upon the totality of the data within the submitted completed clinical trials and literature to support its safe use to visualize malignant tissue during glioma surgery. It is important to note that only high-grade anaplastic tumors (WHO III and IV) exhibit fluorescence and were the only WHO grade studied. In comparison to existing technology, it is not hampered by changes in tumor location due to brain shift during surgery and it does not require interruption of the surgical procedure to acquire images (such as with iMRI). When strong fluorescence is seen, it is correlated with the presence of solid tumor. Due to the infiltrative nature of the disease, the converse is not true; in the absence of fluorescence, tissue may also be positive for malignant cells.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

5-ALA HCl is a chemical substance developed to identify malignant brain tissue during surgery to aid in removal of tumor ("surgical tool"), where possible, to achieve maximal safe resection. 5-ALA HCl was granted orphan drug designation.

Gliomas are a lethal brain tumor which are highly vascular, infiltrative (difficult to observe tumor-normal brain interface), with tumor heterogeneity (low and high-grade elements and satellite lesions within normal brain tissue. The tumor dissemination can cross midlines but is limited to CNS without distant metastases. The ability to identify tumor during surgery is critical to improve the extent of resection and the prognosis for patients with these tumors. Current neurosurgical tools available, such as neuronavigation and iMRI, have their limitations of use. Current treatments have not really improved overall survival for these patients.

The submitted evidence describes the benefit of the product in terms of its strong positive predicative value. There is a solid correlation between fluorescent areas and presence of tumor; however the converse is not true. The absence of fluorescence does not necessarily correlate to absence of tumor. The product works best at identifying the more anaplastic lesions, WHO Grades III and IV, but less so in WHO Grades I or II or other brain lesions that have radiologic findings similar to gliomas on MRI.

The randomized study showed an increase in the extent of resection using 5-ALA compared to the standard conventional surgical procedure and although the studies presented demonstrate a trend upwards in neurologic deficits in the treated arm these returned to baseline within the first post-operative month. The more recent literature has shown that the rate of neurologic deficit is similar to conventional surgery.

It is expected that the product will be able to facilitate disease visualization intra-operatively in conjunction with other neuro-monitoring methods without additional safety concerns.

Dimension	Evidence and Uncertainties	Conclusions and Reasons

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Gliomas are tumors that arise from glial or precursor cells and include astrocytoma, glioblastoma, oligodendroglioma, ependymoma, mixed glioma, malignant glioma, not otherwise specified (NOS), and a few rare histologies. They are infiltrative in nature and cross midline structures often appearing beyond the image seen on MRI making tumor-free margins during resection unrealistic. • The incidence of the disease is 5 to 10 cases per 100,000 persons per year and more than 14,000 new cases of GBM are diagnosed in the United States each year. • The most important prognostic factors for glioblastoma are extent of tumor resection, age at diagnosis, and Karnofsky performance status. • Even with current treatments, survival has not been greatly improved with only small increments (months) of gain. • Recurrence is common in patients with GBM. Greater than 85% of all recurrences are within 2.5cm of the surgical margins; therefore the initial resection is critical. Only 20% of these patients are candidates for additional debulking surgery	This is a lethal disease with a median survival of 15 months. The 5-year survival in the US is <5%. Current treatments have not really improved overall survival for these patients. The ability to identify tumor is critical to improve the extent of resection which in turn should improve the prognosis for these patients.
Current Treatment Options	• Primary treatment is surgical resection to the maximal safe resection possible followed by concurrent chemotherapy and post-operative radiation with temozolmide chemotherapy continuing after completion of radiation therapy. Electric field based loco-regional, antimitotic treatment modality is another post-operative treatment modality. • Intra-operative tools for assessment of tumor include the following, all of which have limitations: o Neuronavigation with registration to pre-operative MRI or	Surgical treatment is complicated by the diffusely infiltrating nature of the malignant gliomas, the need to avoid damage to eloquent cortical areas during surgery, and the problem of removing healthy tissue taken as tumor. It is inherently difficult to define residual tumor during surgery. 5-ALA can identify areas of tumor at the margin and in anaplastic foci

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	PET imaging o Intra-operative MRI (iMRI) o Intra-operative ultrasonography o Sensory-motor mapping/awake craniotomy • For recurrent disease the options include: o Second surgical procedure with or without the use of carmustine wafer implantation (Gliadel Wafers) o A radiation boost to area of recurrence o Salvage chemotherapy, usually bevacizumab or other investigational therapies o TTFields (tumor treating fields), an electric field based loco-regional, antimitotic treatment modality	within more "benign" tumors. As an adjunct to good surgical judgement and use of appropriate neurosurgical tools, it is a method to allow the surgeon information regarding the presence of tumor cells in areas of ambiguity.
Benefit	• Use of 5-ALA during glioma surgery allowed for a greater extent of resection (64% 5-ALA vs. 38% white light) • The presence of fluorescence correlates well with presence of tumor. The PPV was 96-98% in all the studies reviewed • The ability to see borders offers an opportunity for selective sampling of the invading cells which appear to be different from the center of the tumor • For patients with non-operable tumors, stereotactic or open biopsy is performed for tissue diagnosis, so the high PPV would let surgeon identify the most malignant area within the tumor where the likelihood of obtaining an adequate tissue sample is higher, thus reducing the number of passes needed, reducing the risk of sampling error and possible under-grading. • For patients with low-grade gliomas, in whom the risk of malignant	The use of 5-ALA to delineate the tumor is useful to improve the rate of complete resections and prognosis for patients, and obtain adequate tissue for more precise neuropathological grading for subsequent treatment.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	transformation exist, may identify anaplastic foci within the low-grade mass reducing the risk of under-grading and undertreating these patients. • There were no serious drug related adverse reactions seen in the randomized trial or in the European safety update 2015. • Non-serious adverse drug-related reactions the were seen included photosensitivity in 2 patients, transient elevation of liver function tests, hypotension, pyrexia • Post-market data (2015) showed an exposure of >58,000 patients to the drug without any unexpected adverse events and no actions were taken for a safety signal.	
Risk	• There was a trend toward risk of greater neurologic harm resulting from the surgical procedure in the 5-ALA arm • Although 5-ALA is correlated with tumor when the tissue fluoresces, (PPV near 100%), there is also a high rate of tumor in non-fluorescent areas leading to false negatives (80%). • 10% of patients who received the study drug were not included in the efficacy analysis because their histopathology was not WHO Grade III or IV. For these patients, the pathology was not known at the enrollment phase as pre-operative stereotactic biopsy was not done and enrollment was based on MRI findings.	Although there seems to be an increase in neurologic symptoms in the immediate post-operative period, these findings improve with time and persistent new neurologic deficits are no greater than conventional surgery. Neurological deterioration after surgery occurs in 13-26% of all patients with 30-60% experiencing post-op seizures. Patients also exhibit fluctuation of neurologic symptoms throughout the course of the disease. With the use of newer technologies to monitor patients during surgery, injury to critical areas can be avoided. Although there was a risk of greater morbidity from more aggressive surgery this may be countered by surgery being more

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		accurate. Patients without a tissue diagnosis of WHO Grade III or IV pre-operatively may receive 5-ALA, and 5-ALA is not taken up in lower grade tumors or metastatic disease. These patients will still require surgical resection for their tumor. The drug appears to be safe even in this population.
Risk Management	• No risk management issues were identified for the drug. • There are technical aspects to fluorescent-guided surgery that may require additional training.	The drug has a favorable safety profile for its indicated use and patient population. Education of neurosurgeons via labeling to the limitations of the 5-ALA.

2 Therapeutic Context

2.1. Analysis of Condition

Gliomas are primary brain tumors arising from neuroglial stem cells. They have been classified on the basis of the cell of origin and assigned WHO grading I-IV based on the degree of anaplastic change and malignant potential. In 2016 the WHO reclassified diffusely infiltrative gliomas on the basis of their natural histories and response to treatment/outcomes. The resulting system now has three classes: (IDH)-mutant, 1p/19q co-deleted tumors with mostly oligodendroglial morphology that are associated with the best prognosis, IDH-mutant, 1p/19q non-co-deleted tumors with mostly astrocytic histology that are associated with intermediate outcome; and IDH wild-type, mostly higher WHO grade (III or IV) tumors that are associated with poor prognosis.

GBM's are microscopically different from lower grade tumors due to their highly vascular proliferation with areas of necrosis and their infiltrative nature (difficult to observe tumor normal brain interface) with tumor heterogeneity (low-grade elements and satellite lesions). Glioblastoma cells infiltrate significant distances across white matter away from radiographically and clinically evident primary masses making it difficult to determine the extent of tumor present.

Gliomas account for about 30% of all brain tumors and the 80% of malignant tumors in adults. There is an incidence of gliomas of 6.6 per 100,000 people of which about half were glioblastomas. The incidence of gliomas in general increases with age, with the most pronounced increase in glioblastoma incidence (per 100,000 people) ranging from 0.15 in children and 0.41 in young adults to 13.1 in those aged 65–75 years and 15.0 in individuals between 75 and 84 years of age. Many environmental factors have been studied (i.e. cell phone use) but only exposure to ionizing radiation at a therapeutic dose has been identified as a causative factor. Gliomas have been associated with certain familial syndromes such as Neurofibromatosis types 1 and 2, Li-Fraumeni syndrome and Turcot's syndrome.

There is a high morbidity and mortality associated with the disease. Population based studies GBM show a median survival of 42% at 6 mos and 18% at 1 year. 3-5% of patients will survive 3 years. In the US the 5-yr survival rate is 5%. Current Rx (surgery + Chemotherapy + Radiation Therapy) shows only a 14-month median survival and overall survival has not changes in 40 years. A patient living longer than 3yrs is considered a long-term survivor.

Prognosis depends on tumor grade and histology. Additional prognostic factors that influence

outcome include: patient age (younger is better), KPS status, tumor type and location, the extent of resection possible, and presence or absence of genetic markers (such as MGMT, IDH1, promoter TERT and EGRF).

2.2. Analysis of Current Treatment Options

There are currently no FDA approved drugs for visualization of malignant glioma during surgery. The drugs approved for GBM are for post-operative therapies either concurrent with radiation and/or in the adjuvant setting. There is an FDA approved device for treating newly-diagnosed GBM following maximal debulking surgery in combination with temozolomide, the Optune device by Novocure. This device allows for alternating electric field therapy following standard brain radiation with concurrent temozolomide. In a randomized trial it was shown to increase PFS and OS. For recurrent disease it is used as monotherapy after surgical and radiation options have been exhausted.

Surgery is the mainstay of treatment and establishes histological diagnosis, provides symptomatic relief of mass effect, results in recovery of neurological function depending on location of tumor, reduces the number of tumor cells to facilitate the effect of adjuvant therapy, and provides tissue material for molecular analysis. With surgical resection alone, median survival is approximately 6 months. The primary goal of surgical resection is to remove abnormal tissue to the maximal safe limit, typically for this tumor that means a "debulking" procedure rather than complete removal. There are several tools available to the neurosurgeon during the surgery to aid in localizing and identifying tumor. The most commonly used technique is neuronavigation with registration of images from the pre-operative MRI, PET, or ultrasound. These techniques have limitations due to brain shift when the dura is opened and the tumor is exposed. Differences of up to 2cm are known to occur. Intra-operative MRI or ultrasound has been used to alleviate the problem of brain shift, but these require interruption of the surgical procedure to acquire images, are costly, and are not widely available.

For patients who are not candidates for surgical resection, either due to age, co-morbidities or location of tumor, biopsy is recommended to confirm tissue diagnosis and plan treatment.

Following surgery, whole brain radiation and concomitant chemotherapy with subsequent adjuvant chemotherapy is given. Recurrences are common and are treated with a second surgical procedure (where indicated), rescue chemotherapy, or TFF (alternating electric field therapy).

Despite advances in treatment with the addition of chemotherapeutic agents and radiation therapy to surgical resection, the overall survival remains poor.

Table 1: Summary of Treatment Armamentarium Relevant to Proposed Indication

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
FDA Approved Treatments for Glioma imaging						
None						
Other Treatments – used off label for identifying brain tumors						
Fluorescein	Diagnostic angiography or angioscopy of retina and iris vasculature, eye trauma diagnosis, Ophthalmic surgery, lacrimal drainage diagnosis	2003 2006 2008 2015 2016	The normal adult dose of FLUORESCITE Injection 10% (100 mg/mL) is 500 mg via intravenous administration.			(b) (4) Published literature and NCT trial for brain tumor identification is available. First described used in 1948 to localize brain tumors.
Indocyanine Green (ICG)						(b) (4) . Several publications using ICG for brain tumor surgery.

NCCN 2016 Guidelines: do not recommend use of 5-ALA as an intra-operative tool

- Maximal safe resection where feasible with goal for image-verified complete resection
  - With or without Carmustine wafers
  - If not safely resectable the stereotactic or open biopsy, partial resection
- Fractionated external beam RT
  - 1p19q deleted would receive adjuvant CT (PCV or temozolomide)
  - 1p19q non-deleted would receive and temozolomide
  - Anaplastic would receive RT or CT or supportive care
- GBM age <70 with good KPS Standard brain RT with adjuvant temozolomide and ETT (alternating electric field therapy)
- GBM <70 with poor KPS would get brain RT or CT or supportive care
- Age >70 with good KPS would receive same as above based on molecular characteristics

- The EOR should be judged on the post-operative MRI performed within 72 hours and used as a baseline to inform tumor progression and assess further therapeutic intervention

EANO recommendations: 2014, recommend use of 5-ALA with intra-operative neuronavigation, iMRI, and functional mapping to maximize the extent of resection.

- MRI is the preferred imaging method.
- For WHO grades III and IV resection or biopsy followed by radiotherapy and/or chemotherapy
- For progression of disease resection, rescue chemotherapy with bevacizumab
- Routine use of surgical navigation systems housing functional MRI datasets when available, intraoperative MRI, and intraoperative functional monitoring.
- Fluorescent dye 5-aminolevulinic acid (ALA) helps to visualize glioblastoma tissue during microsurgical tumor resection.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

This drug is not a new molecular entity. It is not currently marketed in the US however it is available in Europe, Japan, and Australia/New Zealand.

3.2. Summary of Presubmission/Submission Regulatory Activity

The sponsor has submitted data from clinical trials conducted in Germany from 1999-2005 and provided supportive literature that is more current. There were no discussions with the sponsor regarding clinical study designs or requirements as they had been completed prior to the time of submission of this NDA.

Orphan-drug designation granted: January 15, 2013

Priority Review: yes

Sept. 22, 2014: pre-IND meeting to discuss plans for the submission of an NDA for Gliolan Sponsor provided a summary table of available non-clinical safety data to support the clinical use.

- The Agency agreed that no additional carcinogenicity studies would be needed.
- The need for further reproductive toxicology studies would be a review issue. The company was directed to our guidance if they wished to request a waiver.
- The Agency agreed to no additional non-clinical testing was needed to address

drug-drug interactions

- Size of the safety data base was acceptable. The Agency asked the sponsor to include post-marketing safety experience.
    - The Agency informed the sponsor that it may be possible to obtain the necessary evidence of clinical usefulness from existing data from the medac studies and/or from the medical literature. The data would need to support improved delineation of tumor margin as an indication of clinical usefulness.
- The sponsor was informed that a determination would be made by the Office of Combination Products as to whether Gliolan and the surgical microscope should be developed as a combination product. CDRH stated that because modifications to a traditional microscope are needed including a sophisticated combination of excitation and emission filters with slightly overlapping transmission integrated into its optical configuration,, a microscope needed to be identified and concurrently developed for approval for this indication. The overall safety and effectiveness of the microscope will be established in conjunction with its use with the new drug for the proposed indication

July 23, 2015: pre-IND meeting

- CMC issues agreed upon: Ph. EUR test methods are equivalent to USP methods, we agreed that for oral powder for (b) (4), assessing microbiological quality using USP <61> and USP <62> is acceptable, The proposed DP acceptance limits for impurities are (b) (4) relative to the DS limits and to the batch and stability data supplied.
- Non-Clinical issues: recommended that the sponsor perform in vitro studies of the ability of 5-ALA to act as a substrate or inhibitor of drug metabolizing enzymes and transporters, perform literature searches to identify if there are specific populations of patients that are known to have sub- or super- activity of PEPT2 and estimate the impact of co-administration on 5-ALA exposure, recommended that the sponsor acquire data in subjects with renal impairment and subjects with hepatic impairment.
- Clinical: Sponsor was asked to submit all QT prolongation data sets, provide information regarding any unpublished Gliolan trials, and provide evidence for Gliolan use in primary and recurrent tumor debulking.

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- PREA was not needed due to designation as an “Orphan” product.
- The sponsor proposed a REMS approach and was asked to submit all training

materials, list of additional providers required to take the training, how the adequacy of the training program was determined, criteria to determine a provide has achieved the knowledge and skill needed to use the product

3.3. Foreign Regulatory Actions and Marketing History

This product was approved for use in Europe in 2007 for the following indication:

"Gliolan is indicated in adult patients for visualization of malignant tissue during surgery for malignant glioma (WHO grade III and IV)."

Refer to the Sponsor's Development Safety Update Report (DSUR) Section 11, ('Safety Findings from Marketing Experience')

It was approved in Japan in 2012 following a Japanese trial and supportive evidence from the European experience.

In Australia, the drug was approved in 2013 for the following indication: *". . . adult patients for visualization of malignant tissue during surgery for malignant gliomas that are glioblastoma multiforme (GBM) on preoperative imaging, and who are intended for resection of the tumor".*

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The results of the OSI data confirmation were not available at the time of this review

4.2. Product Quality

The CMC review is ongoing.

4.3. Clinical Microbiology

No issues identified and the reviewer found the product approvable.

4.4. Nonclinical Pharmacology/Toxicology

Nonclinical pharmacology/toxicology studies completed suggest there are two concerns.

One is photosensitivity and is dependent on the 5-ALA dose, the light dose and the tissue

layer being examined. At high plasma concentrations of PpIX like those reached in experimental situations after systemic (oral) administration, phototoxic skin reactions have been observed. According to this data, the skin should be most sensitive to possible phototoxic reactions 4 to 8 hours after ALA administration.

The other is the potential for hepatotoxicity. After oral administration of 30-60 mg/kg of 5-ALA, transient elevations in ALT, GGT and bilirubin were seen in 30-50%.

4.5. Clinical Pharmacology

4.5.1. Mechanism of Action

5-ALA is a natural biochemical precursor of heme that is metabolized in a series of enzymatic reactions to fluorescent porphyrins, particularly PpIX. 5-ALA synthesis is regulated by an intracellular pool of free heme via a negative feedback mechanism. Administration of excess exogenous 5-ALA avoids the negative feedback control, resulting in an overload of the cellular porphyrin metabolism, and accumulation of PpIX in various epithelial and cancer tissues. Malignant glioma tissue (WHO-grade III and IV, e.g. glioblastoma multiforme, gliosarcoma or anaplastic astrocytoma) has been demonstrated to synthesize and accumulate porphyrins in response to 5-ALA administration. The concentration of PpIX is lower in white matter than in cortex and tumor, and 5-ALA induced PpIX formation is significantly higher in malignant tissue than in normal brain. The preferential accumulation of 5-ALA within malignant glioma cells is felt to occur because of decreased levels of ferrochelatase (a heme production enzyme that produces heme with the addition of iron) and selective uptake by an ATP-binding cassette transporter. A reduced ferrochelatase activity like that found in tumor cells is associated with a disproportionately large accumulation of PPIX. The selectively higher accumulation of this substance in tumor tissues results in a stronger fluorescence of these tissues than of adjacent healthy cells of the same tissue type, making it possible to see the tumor.

In the presence of visible light, fluorescence of PpIX (photodynamic effect) in certain target tissues can be used for photodynamic diagnosis. After excitation with blue light (λ = 400-410 nm), PpIX is strongly fluorescent (peak a t λ =635 nm) and can be visualized after appropriate modifications to a standard neurosurgical microscope. Fluorescence emissions can be seen as red or pink in areas with solid tumor and tumor cells, whereas normal brain tissue reflects blue.

PpIX fluorescence is limited to epithelial tissue layers not only because of selective accumulation of PpIX resulting from differences in metabolism (see above) but also because of different depths of penetration of light into tissue. The smallest depth of penetration is 1-2 mm, which is found for a wavelength of 400 nm, and it increases with increasing wavelength (e.g. at

λ=630 nm it is 5 mm). Therefore it is equivalent to surface mapping of the visible portion of the tumor.

4.5.2. Pharmacodynamics

5-ALA is detectable in plasma only for a short time after administration (< 24hours)

4.5.3. Pharmacokinetics

The optimal time for observation of fluorescence in the tumor is determined by 5-ALA uptake and metabolism to PpIX, conversion of PpIX to heme and the type of tissue. In an animal model, the fluorescence maximum was reached at 6 hours after intravenous administration and had decreased by 9 hours. In humans a dose-efficacy relationship between the dose levels and the extent and quality of fluorescence in the tumor core was present; the highest dose of 20 mg/kg was the most effective. Considerable variability in fluorescence intensity was observed for the dose of 20 mg/kg. Doses higher than 20 mg/kg and between 2mg/kg and the chosen dose were not studied.

Under violet-blue excitation light, and to a lesser extent under white light, the intensity of PpIX fluorescence emitted by the tissue surface decreases continuously due to photochemical decomposition of PpIX called photobleaching. After excitation with light (λ=400-410nm), the half-life of PpIX is approx. 15-20 minutes. It is dependent on the intensity of the irradiating light, distance from the operating microscope and the associated light source. In ex vivo studies on glioma biopsies a decrease in PPIX fluorescence to 36% of the baseline value was not observed under violet-blue excitation light until after 25 minutes and under white light until after 87 minutes. [1]
There are no studies that examined the effect of hepatic impairment on the PK of 5-ALA and there are no studies that examined the effect of renal impairment on the PK of 5-ALA.

From a clinical pharmacology perspective, the application is approvable.

4.6. Devices and Companion Diagnostic Issues

The use of this product requires adaptation of existing Class I exempt operating microscopes. They must be fitted with filters of appropriate excitation and capture wavelengths in order to enable the surgeon to see the fluorescence. The regulatory issues relating to the modifications to the microscopes have been reviewed in CDRH Division Surgical Devices/General Surgery Branch 1 in 2014 and with the submission of this NDA. CDRH had requested the applicant provide information on all the microscopes used in the clinical trials and the modifications that were made to enable visualization of fluorescence.

For this NDA submission, it was decided that a generic device labeling would be permitted. CDRH reviewers have requested the following language be included in the labeling and approval.

Gleolan is appropriate for use with operating microscopes adapted with a blue light emitting light source (power density 40-80 mW/cm^2) and filters for excitation light of wavelength 400 to 410 nm, and observation at wavelengths of 620 to 710 nm.

4.7. Consumer Study Reviews

This product will be administered by trained medical personnel in a hospital setting; therefore consumer study reviews are not applicable.

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 2 Lisiting of Clincal Trials Relevant to this NDA

Appears this way on original

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
ALS-3	Prospective, open-label, randomized, multicenter Phase 3 Central neuropathologist and neuroradiologist blinded to patient assignment Title*: Fluorescence-guided resection of malignant*	20mg/kg 5-ALA given once orally 4 hours prior to surgery	Completeness of resection on post-op MRI or % of patients without residual contrast enhancement Progression free survival at 6 months	Single dose followed by surgical resection with or without use fluorescence F/U every 3 months until 18 months or death	Enrolled N=415 Efficacy N=349 Safety N=374	Patients with a unilocular contrast enhancing brain lesion consistent with a malignancy glioma for whom surgical resection was indicated, with findings of WHO grades III-IV malignant glioma on final pathology	Multicenter Single nation (Germa 19 centers

	gliomas with 5-Aminolevulinic acid (5-ALA) vs. conventional resection						
			Studies to Support Efficacy				
ALS-28	Prospective, single-arm, uncontrolled multi-center phase II study Title: *Clinical Phase II Trial of 5-Aminolevulinic Acid Hydrochloride (5-ALA, 5-ALS) for Fluorescence-guided Resection of Malignant Gliomas* Central neuropathologist and neuroradiologist blinded to patient treatment	20mg/kg 5-ALA given once orally 3 hours prior to surgery	The primary endpoint was to determine the positive predictive value of tissue fluorescence, defined as the percentage of patients showing positive tumor cell identification in all biopsies taken from areas of weak and strong fluorescence. Secondary Endpoints: • Calculation of the PPV of tissue fluorescence at the biopsy level • fluorescence intensity measured spectrometrically, tumor cell quantity and histological differentiation • Evaluation of the simplification	Single dose followed by surgical resection with use fluorescence Follow-up for adverse events at 4 weeks	N=39 enrolled N=33 Full-analysis Set N=36 for Safety analysis	Patients with primary GBM who were candidates for surgical resection	Multicenter, single nation (Germa 4 centers

			of resection using of fluorescence-guided resection • Assessment of the location of residual fluorescence observed intraoperatively (infiltration of eloquent structures) by neuronavigation and comparison with contrast enhancement p.o. MRI				
ALS-30	Prospective, single-arm, uncontrolled multicenter phase II study Title: *Clinical Phase II Trial of MC 506/1 (5-Aminolevulinic Acid hydrochloride, 5-ALA, 5-ALS) for Fluorescence-Guided Resection of Malignant Gliomas in Progression*	20mg/kg 5-ALA given once orally 3 hours prior to surgery	The primary endpoint was to determine the positive predictive value of tissue fluorescence. Secondary: • Calculation of the PPV of tissue fluorescence at the biopsy level • Percentage of patients without residual tumor. • Overall Survival • Observation of changes in neurological	6 months following enrollment of the last patient	N=40 enrolled N=36 Full Set Analysis N=40 for Safety Analysis	Patients with recurrent GBM requiring a second surgical procedure Patients must have undergone previous surgery including open craniotomy for newly diagnosed glioma plus standard radiotherapy.	Multicenter single nation (Germany), 4 centers

	Therapy		status before and after re-resection				
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)							
ALS-32	Prospective, open-label, single-arm	20mg/kg 5-ALA given once orally 4 hours prior to surgery	No efficacy endpoints Safety endpoints only	Long-term follow-up (until date of death, but for not more than up to 6 weeks after surgery of the last evaluable patient	N=245 enrolled N=243 for safety analysis	Patients with primary or recurrent GBM	Multi-center 19 sites throughout Germany
ALS-8	Prospective, dose-escalation study	Dose escalation study using 2, 20 and 20 mg/kg					
Literature Review	12 papers selected systematically All were prospective, open-label, single-arm	20mg/kg prior to surgery	Variable	Variable	n/a	Primary or recurrent Gliomas	Usually single center trials

5.2. Review Strategy

This reviewer assessed the protocols from the two phase 2 and single phase 3 trials and corresponding articles submitted as literature to support the product approval. There are multiple sections of this reviewer template that are not applicable to the review of this product due to the limited prevalence of the disease (i.e. Orphan status), and it approval throughout the world that has resulted in the widespread use and adoption of the product as standard of care.

The sponsor did not seek a pediatric indication nor did they submit pediatric data.

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. Fluorescence-guided resection of malignant gliomas with 5-Aminolevulinic acid (5-ALA) vs. conventional resection

6.1.1. Study Design

Overview and Objective

The objective of this study was to determine the efficacy and safety of fluorescence-guided resection of malignant gliomas with 5-Aminolevulinic acid (5-ALA) (FL-group) compared to conventional resection (WL-group) and to assess the clinical usefulness of this method.

Trial Design

The study was originally approved in 1998, with 3 amendments made in 1998, 2000 and 2002. The study was a prospective, randomized, multi-center, parallel-group with a comparison of standard-of-care surgery under normal operating conditions versus use of blue light for fluorescence detection. All patients were to receive post-operative radiation therapy. (At the time of the study, temozolomide was not in widespread use so chemotherapy was not required). Surgery, using other potential techniques for optimizing tumor localization except neuronavigation was not allowed. The surgeon was not blinded to treatment arm assignment creating a potential for operator bias, however all histopathology and radiology readings were blinded to treatment arm.

Patients were enrolled based on pre-operative MRI findings consistent with a radiological suspicion of a unilocular malignant glioma with a distinct ring- or garland shaped, contrast-enhancing tumor structures and a core area of reduced intensity on MRI (tumor necrosis) with absence of a significant portion without contrast enhancement (exclusion of secondary malignant gliomas). The location of the tumor had to be such that the patient would be a candidate for complete gross resection. Only primary GBM appearing lesions on MRI without prior treatment were included. In addition, Karnofsky Performance Status was required to be $\geq$ 70%. Age was limited to 18-75.

Patients were excluded if the tumor location was in the mid-line, basal ganglia, cerebellum or brain stem. A history of porphyria or hypersensitivity to porphyrins excluded the patient, as did renal insufficiency or hepatic insufficiencies. Existing or planned pregnancy or lactation or inadequate contraception also excluded patients.

Reviewer Comment: Few of the patients had a pre-operative biopsy performed, so the histopathology of the tumor was not known until after surgery. This resulted in patients receiving the study drug who did not meet the inclusion criteria for the Full-Analysis Set. An AI letter was sent to the applicant regarding the efficacy of 5-ALA in patients excluded from

analysis but who received the drug and were found to have a lesser grade glioma or metastatic disease. The answer is pending at the time of this review.

Randomization was done 1:1 by surgeon, age (≤ 55, >55), KPS (≤80, >80), and local surgeon's judgement as to proximity to eloquent areas (not central read of MRI).

All patients who were randomized to the study arm were given 20mg/kg of 5-ALA orally 3 hours prior to surgery. This dose choice was based on the findings of an earlier dose escalation study. There was no dose modification.

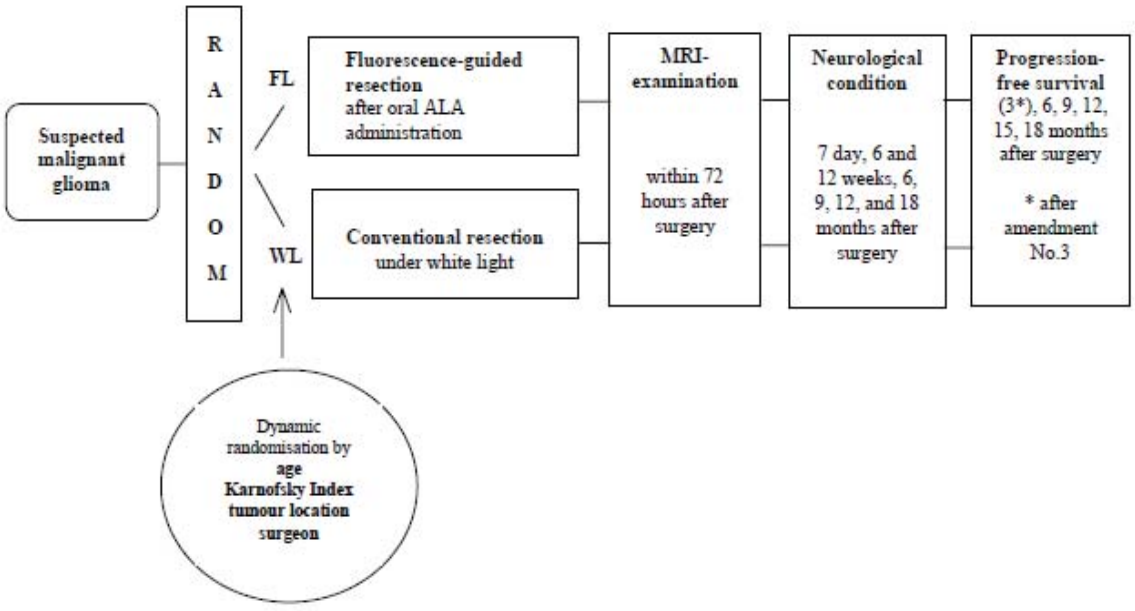


Figure 1 Study Design ALS-3

Tolerated deviations from test deadline	First examination 1 to 14 days pre OP	2 days before OP /	1 day before OP /	Day of Operation /	24 hours after OP /	48 hours after OP /	Day 7 post OP ±1 day	6 weeks post OP ±1 week	3 months post OP ±2 weeks	6, 9, 12, 15 and 18 months post OP ±1 month
Karnofsky Index	x							x	x	x (not 15 months)
NIH score	x					x	x	x	x	x (not 15 months)
Preoperative tumour data	x									
Preoperative symptoms	x									
Dexamethasone treatment	as indicated	at least 3 x 4 mg daily					as indicated			
5-ALA administration **2 – 4 hours before the operation**				**ALA 20 mg/kg KG**						
Haematology	x				x		x			
Serum chemistry	x				x		x			
Urine chemistry	x									
Resection documentation				x						
Histology							x			
MRI	Required					Required (within 72h post OP)			Required	Required
General symptoms (according to CTC List)	x									
Adverse events					x	x	x	x	x	x
Final examination					When study participation ended					

Figure 2 Schedule of Assessments

Study Endpoints

The primary endpoint was: (original)

- The percentage of patients with histologically confirmed malignant glioma (grade III and IV) without residual contrast agent accumulating tumor on the early postoperative control MRI (within 48 hours of the surgery).

Reviewer Comment: MRI assessment of tumor as a surrogate endpoint is challenging in that it is known to underestimate the extent of tumor. The area surrounding the enhancement (frequently described as "edema") has been shown to harbor tumor cells. However it is the standard for assessing completeness of resection in all clinical trials and is part of professional society guidelines.

- Progression-free survival 6 months after primary surgical treatment of a malignant glioma in patients with histologically confirmed malignant glioma (grade III or IV –WHO).

The secondary endpoints were:

- Determination of the overall survival (OS). This will entail a follow up of the patients until death, but not longer than 18 months after primary surgical treatment of the last study patient
- Determination of the progression-free survival (PFS) 9, 12, 15 and 18 months after primary surgical treatment
- Volume of residual tumor.
- Toxicity after oral administration of 5-aminolevulinic acid.
- Neurological condition 7 days and 6 6 and 12 weeks, and 6, 9, 12, 18, and 24-months weeks after surgery.
- Comparison between the results of fluorescence diagnostics (intraoperative residual tumor) and the early postoperative MRI (radiological residual tumor)

Statistical Analysis Plan

The statistical analysis plan consisted of statistical testing of the two primary efficacy endpoints in a defined hierarchical order. Confirmatory testing of the second target criterion was to be performed if and only if fluorescence-guided resection had been shown to be superior to conventional resections as the first test criterion. Each primary efficacy criterion was tested on the nominal two-sided significance level of 5% to maintain the multiple type I error of 5%.

There was an allowance for an Interim Analysis of the first 270 patients. If the first primary endpoint failed to show statistical significance, the study would be terminated for futility. In case of statistical significance, progression-free 6-month survival was planned to be subjected to confirmatory analysis. If statistical significance was reached, the study could be stopped with claim of efficacy. If no statistical significance were attained for the progression-free survival at 6-month visit, an additional 80 patients could be recruited.

Statistical analysis was based on observed values only. No imputation strategies were applied in this study.

Missing data for the primary efficacy criteria were evaluated as patients with residual tumor on MRI or with progression of disease at 6 months ("worst" case scenario).

Reviewer Comment: For purposes of this NDA submission and the visualization claim, the applicant re-analyzed the data to determine the PPV at the biopsy level and therefore the endpoints for which the studies were conducted were relegated to a supportive role.

Protocol Amendments

There were 3 amendments to the original study plan.

- Amendment 1: the secondary endpoints 3 & 4 were changed to neurologic condition a 7 days, 6 and 12 weeks, and 6,9,12,18,and 24 months. In addition, the follow-up period was extended to detection of tumor progression or 24 months after surgery.
- Amendment 2: the age was increased to 72 years, the post-operative MRI was extended to within 72 hours, and revisions based on the new secondary endpoints were made to the efficacy analysis.
- Amendment 3: in 2002, after approval of temozolomide which considered PFS at 6-months as an endpoint, the following was added as a second primary endpoint to be evaluated as discussed in section on statistical analysis plan.

Data Quality and Integrity: Sponsor's Assurance

This study was audited according to an internal audit procedure and a predefined audit plan including Document audits as study protocol, patient information, informed consent, case report forms, clinical study report, trial master file including all critical documents and an Investigator site audit. The audit certificate was included in Appendix 16.1

6.1.2. Study Results

Compliance with Good Clinical Practices

The applicant has provided attestation the studies were done in accordance with GCP.

Financial Disclosure

There were 36 investigators in 19 centers throughout Germany.

Patient Disposition

For the final analysis:

N= 415 consecutive patients enrolled
N=207 randomized to fluorescence arm (FL)
N=208 to white light (WL)

Excluded from Efficacy Analysis: N= 66 (31 in FL arm and N=35 in WL arm)

1. Did not meet histologic Grade III or IV on post-operative central neuropathological review: N=21/207 in FL arm
   N=20/208 in WL arm
2. Did not meet radiologic criteria: N=15 (FL arm=5, WL arm=10)
3. Withdrawal of consent: N=5 (FL=2, WL=3)
4. Did not undergo resection: N=3 (FL arm=2 and WL arm=1)
5. Did not meet inclusion/exclusion criteria other than above: N=2 (1 In each arm)

Full Set Analysis (FAS) or Intent-to-Treat: FL arm: N=176/207
WL arm: N=173/208

Per-Protocol Set: N=329/415 (FL arm=160), WL arm=166)
N=23 (FL=12, WL arm=11 arm) additional patients excluded.

The reasons for exclusion:

1. due to an early death (1 in each arm),
2. a second surgery prior to progression of disease (3 in WL arm),
3. withdrawal of consent prior to 6 month visit (1 in FL and 2 in WL),
4. deviations of time with efficacy evaluation (7 in FL and 2 in WL),
5. early post-operative MRI not assessable (1 in FL and 2 in WL)
6. Lost to follow-up (1 in WL)

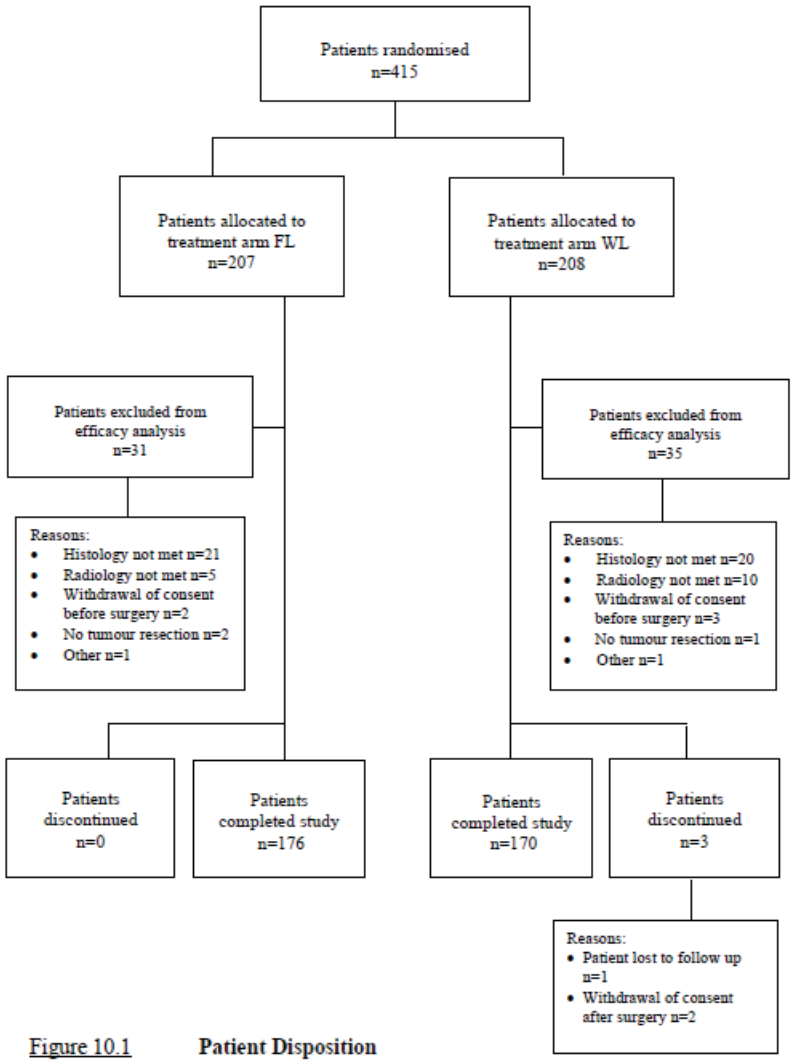


Figure 3 Patient Disposition

Protocol Violations/Deviations

The most frequent deviation was a visit schedule where the imaging study was done out of time window, not performed or CT done instead of MRI post-operatively. Similarly the NIH-Score evaluation was not done within the time window or at all. The distribution of these events was similar in both arms.

There was one patient randomized to control that received 5-ALA but was operated on under

white light only and 19 times where the patient received the study drug but surgery was performed under white light, thus missing the opportunity to capture additional drug performance data. There were 4 times when the device failed.

Table 3 Demographic Characteristics of Study ALS-3

Demographic Parameters[1]	Control Group (N=208)	Treatment arm (N=207)	Total (N=415)
Sex			
Male	131	123	245
Female	77	84	161
Age			
Mean years (SD)	58 (SD 10)	60 (SD 11)	58 (SD 10.5)
Median (years)	60	60	61
Min, max (years)	22-73	19-73	19-73
Age Group			
≥ 19 - < 55 years	61	61	122
≥ 55 years	147	146	293
> 65 - < 75 years	64	59	123
≥ 75 years	0	0	0
Region)			
Europe	208	207	415

[1] Data on race and/or ethnicity were not collected in Germany.

Reviewer Comment: This distribution is representative of the population with the disease however; racial/ethnic differences in survival after primary glioblastoma diagnosis may exist. Information on race/ethnicity was not collected in these trials. Dubrow and Darefsky [2] have stated that "white populations had the highest incidence rates, North American Blacks had intermediate rates, and populations of eastern and southeastern Asian origin had the lowest rates" so the population chosen may not reflect that of the US. Since white populations tend to have a higher incidence of GBM, this may represent the "worst case" scenario.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Tumor location and size are important prognostic factors. Surgeons need to preserve normal tissue to limit a worse neurologic outcome. Avoidance of eloquent areas is critical.

Table 4 Localization of Tumors in ALS-3

	Localization of Tumor		Speech	Motor	Optical
Fluorescence	Eloquent	111	28	54	31
	Non-eloquent	66			
	Unknown	8			
Control (white light)	Eloquent	99	39	41	16
	Non-Eloquent	85			
	Unknown	16			

The distribution between the two arms is similar except when looking at the eloquent area of the brain affected, where the FL arm had nearly twice as many tumors near the optical regions. Although many were considered near eloquent areas, they were all deemed "resectable" on entry to the study.

Table 5 Patients stratified by age, KPS and tumor location provided by applicant

			p-value	Odds Ratio	95% CI
<=55 yrs, <=80%, no	100.0 (1/ 1)	50.0 (2/ 4)	1.0000[2]	. [3]	. [3]
<=55 yrs, <=80%, yes	25.0 (1/ 4)	66.7 (2/ 3)	0.4857[2]	0.17	0.00 - 8.85[2]
<=55 yrs, > 80%, no	80.0 (20/ 25)	66.7 (12/ 18)	0.4805[2]	2.00	0.40 - 10.16[2]
<=55 yrs, > 80%, yes	72.7 (16/ 22)	37.5 (9/ 24)	0.0166[1]	4.44	1.27 - 15.52
> 55 yrs, <=80%, no	60.0 (9/ 15)	0.0 (0/ 6)	0.0186[2]	. [3]	. [3]
> 55 yrs, <=80%, yes	53.3 (8/ 15)	30.8 (8/ 26)	0.1537[1]	2.57	0.69 - 9.55
> 55 yrs, > 80%, no	65.6 (21/ 32)	47.5 (19/ 40)	0.1241[1]	2.11	0.81 - 5.50
> 55 yrs, > 80%, yes	56.5 (26/ 46)	28.9 (13/ 45)	0.0077[1]	3.20	1.34 - 7.63

As would be expected in patients with brain tumors, neurologic symptoms were present pre-operatively. The symptoms found most commonly were headache, impaired motor function, speech impairment, seizures, and these were equally distributed across both arms. The fluorescent group presented with impaired vision 23% versus 16% for the control group, which is consistent with the tumor localization near the optical region of the brain in more patients in the FL arm.

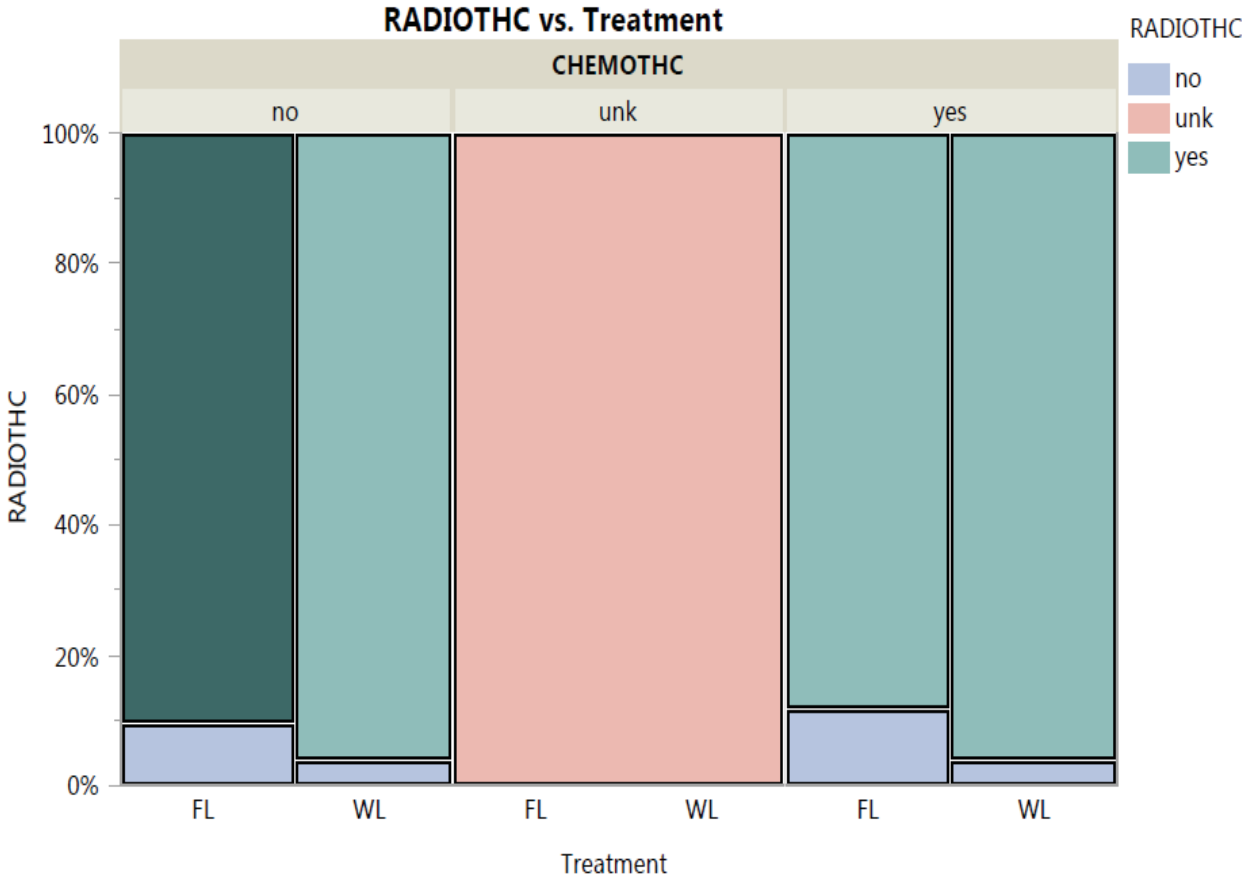
Co-morbidities were similar and again are consistent with the age of the population with the disease. Most frequent were cardiovascular disorders (1/3 of patients in each arm) followed by

diabetes (15-17% in each arm).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Study medication was administered orally under the supervision of the investigating physicians or authorized medical personnel. All patients received dexamethasone prior to surgery and for a brief period posit-operatively per protocol.

Post-operative therapy consisted of radiation therapy and/or chemotherapy. Of 219 patients, 175 (79.9%) received chemotherapy, 195 (89.0%) radiotherapy, 8 (3.7%) other treatments and 34 (15.5%) underwent re-resection of the tumor. Other therapies included different types of local radiotherapy like radioimmunotherapy, GliaSite, Iodine-125-Seeds, palliative interstitial brachytherapy, stereotactic radiotherapy, confocal boost radiotherapy or other treatment modalities as photodynamic laser therapy, nanotherapy, selenium, H15 boswellia acid, laser-thermotherapy, local hyperthermia, or mistletoe. Progression-free survival and overall survival would be influenced by these subsequent treatments. More patients in the control group underwent re-surgery or received other tumor-specific therapies.



Efficacy Results – Primary Endpoint

The original endpoints will be reviewed as they provide support for clinical usefulness, but for purposes of this NDA submission and the visualization claim, the data was re-analyzed to determine the PPV at the biopsy level of 5-ALA in a post-hoc analysis. This will be discussed later in the review with the additional studies used to determine efficacy.

Data Quality and Integrity – Reviewers' Assessment

Primary Endpoint One: Completeness of Resection

Table 6 "Completeness" of Resection

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

At the interim analysis there was a clear difference favoring the 5-ALA arm so the secondary endpoint was studied. When analyzed for age, KPS and location there were more patients without residual tumor if they were young, had a better pre-operative KPS score and had tumors away from eloquent areas favoring the FL arm.

Enhancing the extent of resection can be demonstrated by the number of times the fluorescence was present after complete resection was done under WL. Data was available for studies ALS-28 and ALS-30 where the surgeon stated if there was residual disease under white light and fluorescence at various sites of the resection cavity.

Table 7 Comparison of FL and WL in studies ALS-28 and ALS-30

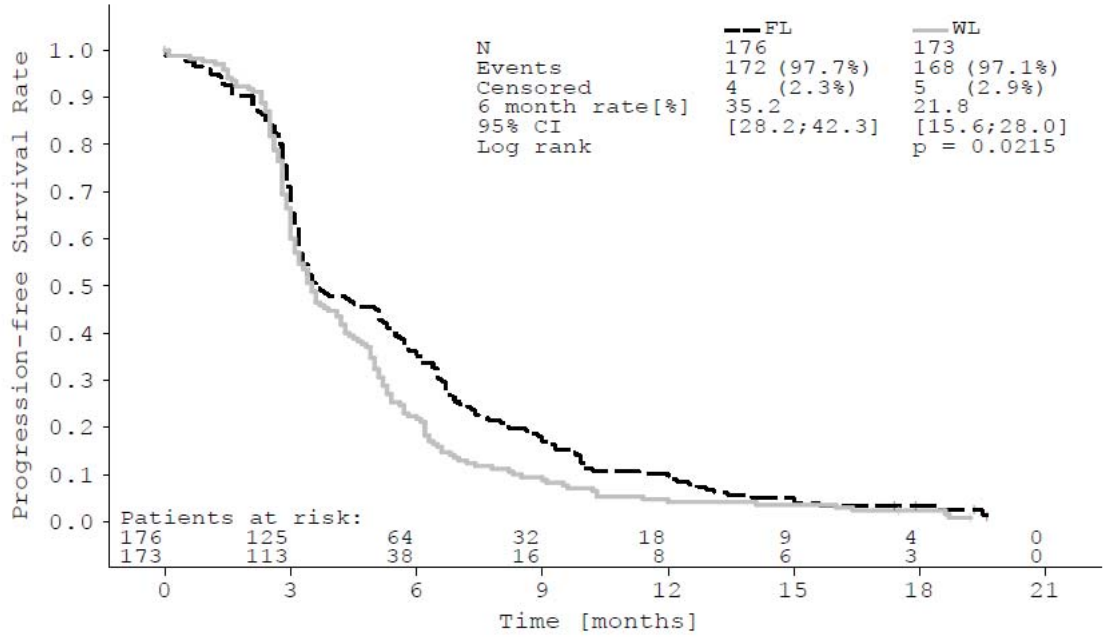
N=108 sites	FL (+)	FL (-)
WL (+)	34 (31%)	5 (5%)
WL (-)	37 (34%)	18 (17%)

Reviewer's comment: In about 1/3 of the sites WL and FL were able to identify abnormal tissue. Fluorescence found additional tumor in about 1/3 of the patients where the surgeon felt it was normal under WL. This demonstrates the utility of 5-ALA to improve the extent of resection if not in an eloquent area.

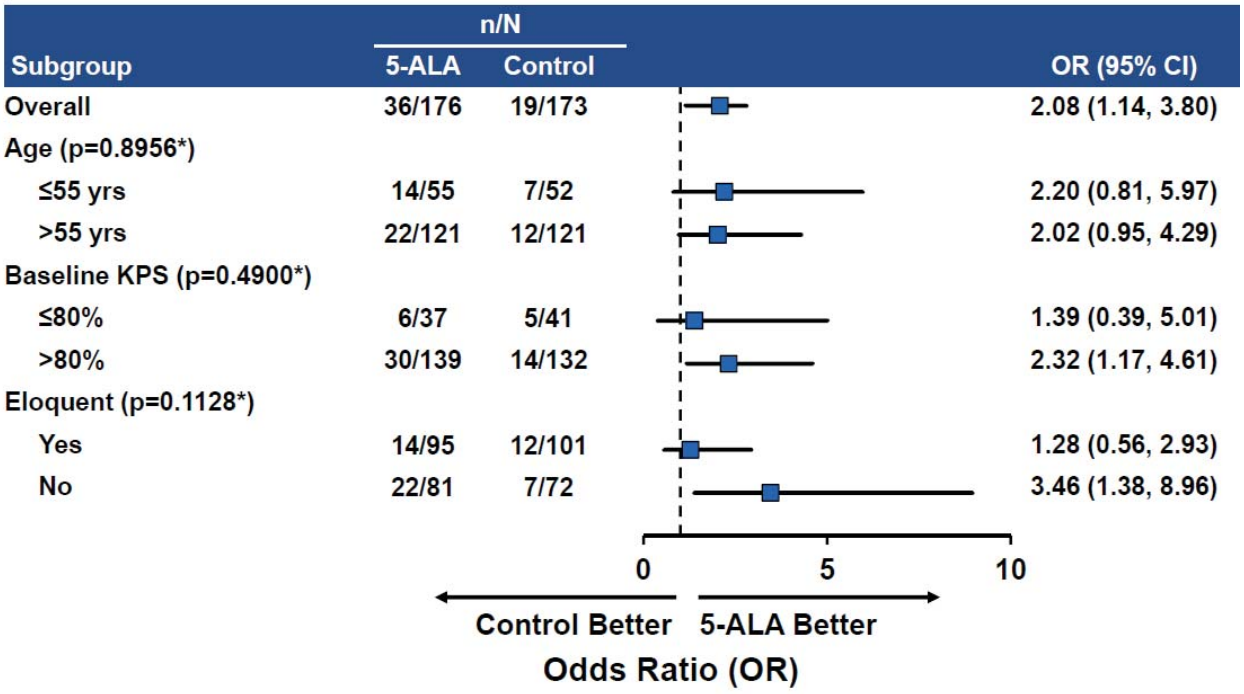
Primary Endpoint Two: Progression Free Survival

The analysis of "progression-free survival at the six-month visit" was performed on a visit-based perspective incorporating all MRI examinations performed within a time window plus/minus one month around the scheduled visit. Tumor progression defined as occurrence of new tumor or increase in volume of residual tumor > 25% on MRI. There was a difference noted at six months with 36% (5-ALA) vs. 22% (WL) alive without progression.

Figure 4 Kaplan-Meier Curve for Progression Free Survival from Sponsor



At the MIDAC meeting the sponsor provided additional information that looked at PFS across the prognostic factors of age, KPS, and location. They presented the following:



n=numbers alive without progression at 6 months.; N=number in group.
*p-value for Breslow-Day test for homogeneity of the odds ratio.; **Exact confidence interval for odds ratio.

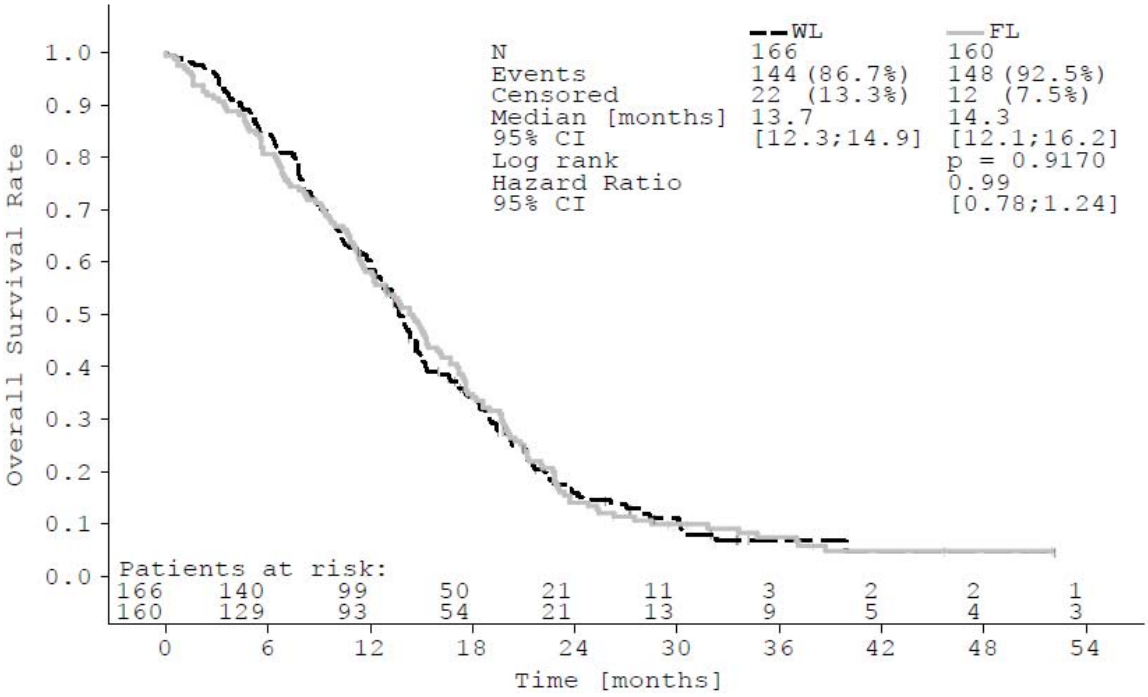
Across all groups there was a benefit in the 5-ALA arm over the control.

Reviewer Comment: This 6-month progression-free survival was based on MRI findings, not clinical findings. This is a problem with the trial design since many patients who experience clinical progression may have only minimal radiological findings and conversely patients with documented radiological progression may have no clinical deterioration. However in clinical practice, physicians routinely use radiologic evidence of progression of disease to define the need for additional therapies.

Efficacy Results – Secondary and other relevant endpoints

1. Determination of the overall survival (OS): Based on follow up of the patients until death, but not longer than 18 months after primary surgical treatment of the last study patient

Figure 5 Kaplan-Meier Curve of Overall Survival from Sponsor



2. Volume of residual tumor.
   The median residual tumor volume for patients in the FL-group was 0.0 cm3 (range 0.0-45.1 cm^3) and for patients in the WL-group 0.5 cm^3 (range 0.0 - 32.6 cm3). In the FL group, a maximum of 81% reduction in tumor volume could be achieved in 95% of patients compared to a maximum of 70% tumor reduction in 95% of patients in the WL-group.

Reviewer Comment: Multiple retrospective studies have shown that reduction in tumor volume by at least 80% is associated with better survival.[3,4,5,6,7]

3. Neurological condition 7 days, at 6 and 12 weeks, and at 6, 9, 12, 18, and 24-months weeks after surgery.
   Neurological progression was defined as deterioration in the NIH sum score by at least 1 point in case of stable or increased corticosteroids

Dose/Dose Response

This section is not applicable.

Durability of Response

This is not applicable for this single use product.

Persistence of Effect

Not applicable.

Additional Analyses Conducted on the Individual Trial

The applicant re-analyzed the data from this trial to determine PPV at the biopsy level for the primary performance measure../

6.2. Clinical Phase II Trial of 5-Aminolevulinic Acid Hydrochloride (5-ALA, 5-ALS) for Fluorescence-guided Resection of Malignant Gliomas (ALS-28)

6.2.1. Study Design

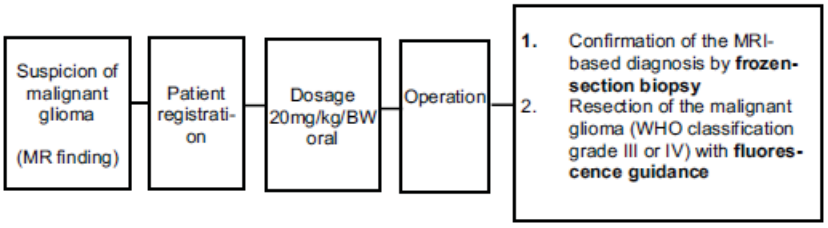
Overview and Objective

The primary objective was to determine the positive predictive value of tissue fluorescence, defined as the percentage of patients showing positive tumor cell identification in all biopsies taken from areas of weak and strong fluorescence.

Trial Design

This was a prospective, single-arm, uncontrolled, 2 center phase II study of an intraoperative diagnostic procedure with central neuropathological and neuroradiological assessment in patients with newly diagnosed primary GBM per MRI criteria.

Figure 6 Study Design ALS-28



Follow-up was 4 weeks.

Inclusion and exclusion criteria were the same as the previously described study. Biopsy selection sites were determined after removal of tumor core and the necrotic tissue (debulking) The surgeon was instructed to select 3 different sites with strong fluorescence to be measured

spectrometrically and biopsied. The surgeon also identified 3 areas of weak fluorescence to measure and sample. If possible, 2 non-fluorescent areas were to measured and biopsied

Parallel treatment with at least 3x4 mg dexamethasone per day for a period of 2 days prior to

and until 2 days following the operation.

Table 8 Study Calendar ALS-28

Tabular Study Schedule **Page1/2**

	Preoperative				Postoperative	
	First exam	**2 days**	**1 day**	**First exam**	**1 day**	**2 days**
Tolerated deviation of test dates (d)	2-5 days preoperative	/	/	/	/	/
Documentation of target/actual times of tests performed (RR, ECG, lab)			X	X	X	X
Patient registration	X					
Karnofsky index	X		X			
NIH score	X		X			X
Preoperative tumour data	X					
Preoperative symptoms	X					
Concurrent diseases	X					
Dexamethasone treatment	Accord. indication	At least 3x4 mg/day		At least 3x4 mg/day	At least 3x4 mg/day	
5-ALA administration (oral) **Application 3 h before inducing anaesthesia (range 2.5 – 3.5 h)**				Dose 20 mg/kg BW orally		
Selection of test areas (see chapter 10)				1. Strong fluorescence 2. Weak fluorescence 3. Non-fluorescent areas extending to fluorescent areas 4. Tumour-distant cortex		
Spectrometry (see chapter 10)				In the selected test areas		
Parenchyma biopsy (PB) (see chapter 10)				In the selected test areas		
Localisation measurement of residual fluorescence (neuronavigation)				X		
Blood pressure (RR) (Measured lying down) Time			X 08:00	t_0 directly before application t_1 30 min after application t_2 60 min after application t_3 120 min after application	X 08:00	
ECG Time			X 08:00	t_0 directly before application t_1 30 min after application t_2 60 min after application t_3 120 min after application	X 08:00	
Resection documentation				X		
pO_2 saturation (Pulsoxymetry)				Intraoperative, continuous		
Blood gas analysis (BGA)				Intraoperative, at least 2 X		
Haematology – blood count Time	X		X	X 12:00 / X 22:00	X	X
Serum chemistry Time	X		X	X 12:00 / X 22:00	X	X
Histology				X		
MRI (tolerated deviation of exam)	X (up to max. 14 days pre-OP)				Within 48 h post-OP (max. within 72 h)	
General symptoms (according to CTC Checklist)	X		X			
Adverse events (according to CTC Checklist)				X	X	X
Documentation of concomitant /adjuvant medication	X	X	X	X	X	X
Final examination						

NIH = National Institute of Health - Stroke Score
MRI = Magnetic resonance imaging
CTC = Common Toxicity Criteria (National Cancer Institute Bethesda/USA)
ECG = Electrocardiogram leads (I, II, III, AVR, AVL, AVF, V_1-V_6)
BGA = Blood gas analysis

Continuation: Tabular study schedule **Page 2/2**

	Postoperative				
	3 days	**4 days**	**7 days**	**14 days**	**4 weeks**
Tolerated deviation of test dates (d)	/	/	/	± 3 days	± 4 days
Documentation of target/actual times of tests performed (RR, lab)	X	X	X	X	X
Karnofsky Index	X		X	X	X
NIH Score	X		X	X	X
Dexamethasone treatment	According to indication				
Blood pressure (RR)			X		
ECG			X		
Haematology, blood count		X	X	X	X
Serum chemistry		X	X	X	X
Adverse events (according to CTC checklist	X	X	X	X	X
Documentation of concomi-tant/adjuvant medication	X	X	X	X	X
Final examination					X

NIH = National Institute of Health - Stroke Score **CTC** = Common Toxicity Criteria (National Cancer Institute Bethesda/USA)
MRI = Magnetic resonance imaging **ECG** = Electrocardiogram – leads (I, II, III, AVR, AVL, AVF, V_1-V_6)
BGA = Blood gas analysis

Neurohistological workup and evaluation was done with by a central histopathologist calculating the percentage tumor cells semi-quantitatively by consensus of two independent examiners from the reference institute for neuropathology and reported using a quartile scale. In addition the histological differentiation was recorded as: solid, infiltrative, necrosis, or normal tissue. The frozen-section diagnosis was performed intraoperatively to verify the MRI diagnosis (malignant glioma III or IV) by the local pathology.

Study Endpoints

The primary objective was to determine the positive predictive value of tissue fluorescence, defined as the percentage of patients showing positive tumor cell identification in all biopsies taken from areas of weak and strong fluorescence.

The secondary endpoints included:

- Calculation of the positive predictive value of tissue fluorescence at the biopsy level, defined as the number of tumor positive biopsies among all biopsies taken from areas of weak and strong fluorescence.
- Evaluation of the quality of the fluorescent and of the non-fluorescent tissue adjacent to fluorescent tissue areas as well as the tumor distant cortex with respect to its
  a) Fluorescence intensity measured spectrometrically
  b) Tumor cell quantity
  c) Histological differentiation (vital, solid, proliferating tumor; infiltrative tumor; necrosis; normal tissue).

- Evaluation of the simplification of resection using of fluorescence-guided resection by the surgeon using a 4-point scale (none, minor, moderate or pronounced effect)
- Assessment of the location of residual fluorescence observed intraoperatively (if there was infiltration of eloquent structures) by neuronavigation and comparison with contrast enhancement (residual tumor) on early postoperative MRI (within 72 h postoperatively).

Statistical Analysis Plan

A sample size of 33 patients in the Full Analysis Set was required to estimate the positive predictive value with a precision of plus/minus 20% expressed as the half length of the associated two-sided 90% confidence interval with a power of 80% assuming the expected positive predictive value to be 90%. Dropouts were to be replaced individually to reach the required sample size

Protocol Amendments

There was one administrative amendment to the original protocol.

Data Quality and Integrity: Sponsor's Assurance

Audit certificate provided.

6.2.2. Study Results

Compliance with Good Clinical Practices

The study was conducted in accordance with ethical principles that have their origins in the Declaration of Helsinki (Somerset West, South Africa 1996) and in compliance with all applicable local regulations and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines

Patient Disposition

Total number of evaluable patients: N=31
Number of patients enrolled: N=39
Patients discontinued and causes: n=8
Non-eligible histology: n=2
Prior to surgery due to elevations labs: n=3
No surgery: n=1 (unable to intubate)
Withdrew consent: n=1
Early study death: n=1

Figure 7 Patient Disposition ALS-28

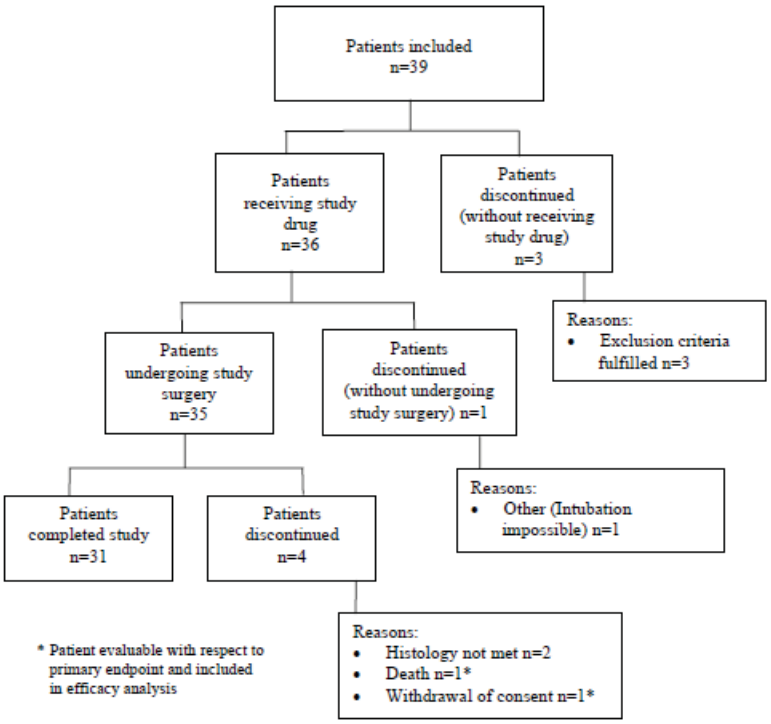


Figure 10.1 **Patient Disposition**

Protocol Violations/Deviations

Protocol Deviations: The most frequent reason cited was a deviation of visit schedule including baseline visit outside window of 2-5 days pre-operatively, IH or KPS not done at all time intervals, missed visits due to radiation therapy given at a distant site. These did not impact the endpoints which were histopathologic correlation with fluorescence.

Table of Demographic Characteristics

Table 9 Demographics Full Set Analysis ALS-28nalysis

	N=33
Age	
≤ 55 years	13 (39%)
55 years	20 (61%)

Mean (SD)	57 (13)
Median	61
Range	21-72
Gender	
Female	15 (46%)
Male	18 (54%)

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

- Median baseline tumor volume was 36.6 cm^3 (1-179cm^3)
- Most tumors were in eloquent areas with a predominance of motor function (42%) followed by speech and vision (each 6%)
- All patients had at least one neurologic finding pre-operatively with headache (36%), seizures (33%), motor (30%) and speech (30%) the most common. Vision complaints occurred in 24% patients.
- Cardiovascular histories in 42%
- Baseline KPS median was 90 and median NIH Stroke Scale was 1 (scale of 1-36)

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

No dose modification was permitted. Study drug was administered by trained medical personnel.

On Day 1 and 2 prior to surgery, patients received 12mg dexamethasone which could be continued into the post-operative period at the neurosurgeon's discretion. There were no restrictions with respect to the common follow up therapies.

Efficacy Results - Primary Endpoint

The primary endpoint of this study is not the endpoint that the sponsor has chosen for this NDA visualization claim. It is the secondary endpoint of PPV at the biopsy level will was evaluated and will be discussed later with combined efficacy evaluation. In addition the correlation between fluorescence intensity and tumor cellularity and histology will be presented as well.

Efficacy Results- Other Secondary Endpoints

- Evaluation of resection simplification using fluorescence: In about two thirds of patients (63.6%) surgeons described a pronounced simplification and in about one third of patients a (30.3%) moderate simplification of resection by use of the fluorescence method. Weak or no simplification was recorded in a single patient.

- Correlation between residual fluorescence/tumor observed intraoperatively and residual tumor on early postoperative MRI:

    - The estimated area of residual fluorescence recorded intraoperatively, corresponded well to volumes of residual contrast enhancement detected on early postoperative MRI.

    - In 65.2% of patients with intraoperatively recorded residual tumor/fluorescence, reference neuroradiology was able to detect residual contrast enhancement.

    - Complete resection of tumor/fluorescing tissue as **assessed intraoperatively by the surgeon was** achieved in 30.3% of patients

    - In 2/10 without residual tumor according to the surgeon's assessment, the MRI showed residual enhancement located at a distance to the resection cavity. In the rest there was no corresponding residual tumor documented intra-operatively.

    - Some of the intraoperative sites with suspected residual tumor were visible only under fluorescence conditions (but not using standard white light). Other positions were suspicious both under fluorescence conditions and using standard white light. Of the 42 sites with suspected residual tumor at surgery, 32/42 were detected only with FL while the remaining 10 could be seen with both.

6.3. Clinical Phase II Trial of MC 506/1 (5-Aminolevulinic Acid hydrochloride, 5-ALA, 5-ALS) for Fluorescence-Guided Resection of Malignant Gliomas in Progression Therapy (ALS-30)

6.3.1. Study Design

Overview and Objective

The primary objective was to determine the positive predictive value of tissue fluorescence, defined as the percentage of patients showing positive tumor cell identification in all biopsies taken from areas of weak and strong fluorescence.

Trial Design

This was a prospective, single-arm, uncontrolled, multi-center (4) phase II study of an intraoperative diagnostic procedure with central neuropathological and neuroradiological assessment in patients with recurrent disease who were candidates for surgical resection.

Inclusion/exclusion criteria were the same as previous studies except that this population had recurrent disease and KPS could be as low as 60.

All patients received a single dose of 20mg/kg 5-ALA 3 hours prior to surgery.

After resection, the tumor bed was examined under white light to delineate areas of pathology and normal tissue for biopsy. The same areas examined under blue light and classified as weak, strong or non-fluorescent and biopsies were taken for each fluorescence intensity (strong and weak). There were very few biopsies taken from non-fluorescing areas.

At the end of the operation the surgeon was to assess whether all fluorescence-positive areas or areas suspicious for tumor under conventional white light had been resected and, if not, to describe the anatomical area of residual tumor. This was to be done to allow a comparison of residual tumor, as determined intraoperatively, with the location of contrast-enhancing tumor on early postoperative MRI.

Follow-up of patients for a period of six months after study surgery with evaluation of the patient's neurological status (NIH stroke score), physical performance (KPS), and laboratory parameters. Survival was determined quarterly thereafter.

Study Endpoints

The primary endpoint was to determine the positive predictive value of tissue fluorescence, defined as the percentage of patients showing positive tumor cell identification in all biopsies taken from areas of weak and strong fluorescence.

The secondary endpoints were:

1. Calculation of the positive predictive value of tissue fluorescence at the biopsy level, defined as the number of tumor positive biopsies among all biopsies taken from areas of weak and strong fluorescence.
2. Percentage of patients without residual tumor.
3. Overall Survival
4. Observation of changes in neurological status before and after re-resection using the NIH Stroke Scale and in the general condition using the Karnofsky Performance Status

Statistical Analysis Plan

A sample size of 33 patients in the Full Analysis Set was required to estimate the positive predictive value with a precision of plus/minus 20% expressed as the half length of the associated two-sided 95% confidence interval with a power of 80% assuming the expected positive predictive value to be 90%. Dropouts were to be replaced individually to reach the required sample size. Exact 95% Clopper-Pearson confidence intervals were provided for estimating the positive predictive value. Analyses were also stratified by fluorescence qualities.

6.3.2. Study Results

Compliance with Good Clinical Practices

As per previous trials.

Patient Disposition

Number enrolled: N=40

Number discontinued: n=5

Number completing surgery: n=36

Lost to follow-up: n=1

Non-eligible histology: n=2

Didn't meet inclusion criteria: n=1

Device failure: n=1

Figure 8 Patient Disposition ALS-30

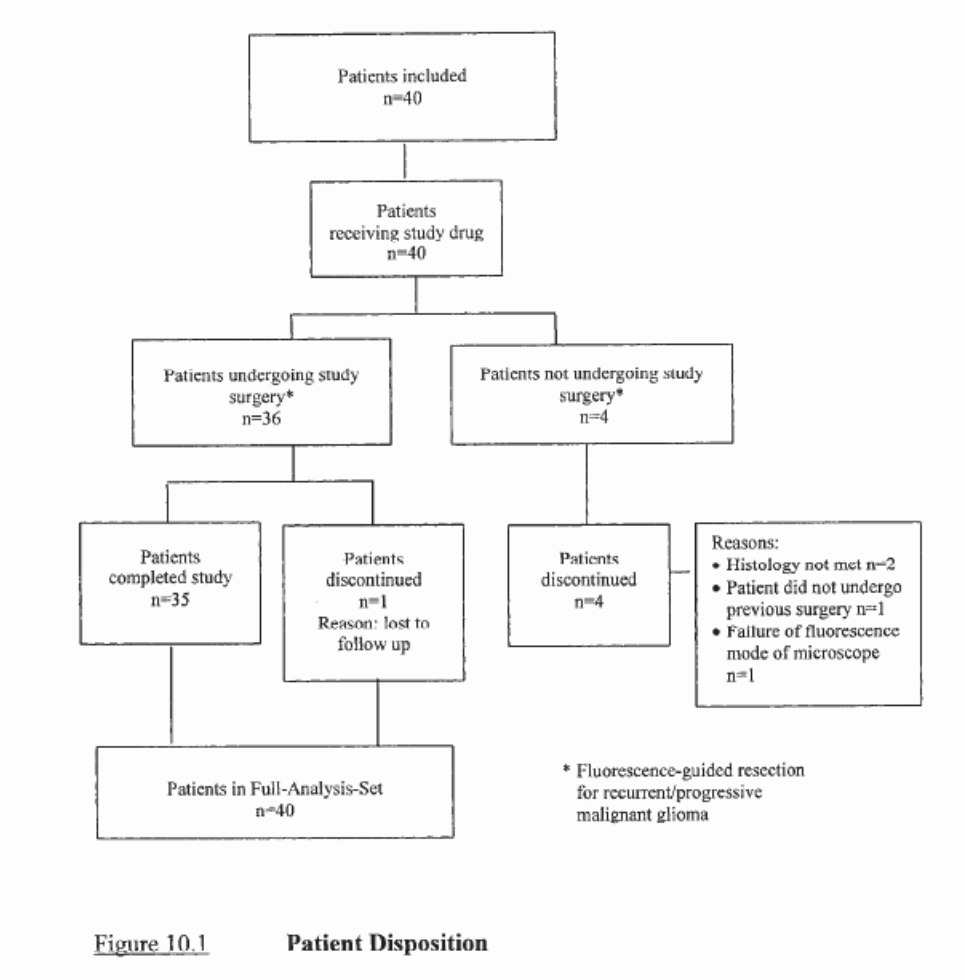


Figure 10.1 **Patient Disposition**

Insert text here.]

Protocol Violations/Deviations

Once again the most frequent protocol deviation was a visit schedule deviation, usually missing a NIH SS assessment or lab evaluation. There were some deviation in time from drug administration to surgery but the median was within the proscribed range. The longest time to surgery was 6.75 hours which is still within the optimal imaging window.

Again, none of these deviations had an impact on the endpoints.

Table 10 Demographic Characterstics ALS-30

Age	

≤ 55 years	17 (47%)
>55 years	19 (53%)
Gender	
Female	11 (31%)
Male	25 (69%)

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

- The localization of tumors affected eloquent areas of the brain, mostly regions with motor function (22.2%), followed by areas with language function (19.4%), other eloquent structures (13.9%), or visual function (8.3%).
- Most patients presented at initial diagnosis with a WHO grade IV tumor (58.3%), predominantly glioblastoma multiforme, or with a WHO grade III tumor (36.1%), mainly anaplastic astrocytoma. However, 5.6% patients presented with a low grade tumor at initial diagnosis, which de-differentiated over time
- Neurologic symptoms present at baseline included: seizures (50.0%), impaired neuro-motor function (44.4%), impaired vision (13.9% of patients), and speech impairment (38.9%) as the most frequently occurring signs and symptoms.
- The most common co-morbidity was cardiovascular disease.
- Most patients were rated with 0 or 1 of 36 possible points on the NIH-stroke scale (0 and 1 point: 36.1% and 13.9 %, respectively). Median score of 1.5.
- The median time interval between initial surgery and study surgery was 14.5 months (range 3 -148 months).
- Most patients underwent one previous surgical intervention (75%). There were some patients with up to 5 previous surgeries.
- 39/40 patients had received radiation therapy and 2/3 had received some type of chemotherapy

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

For at least 2 days prior to the operation all patients should have received 3 x 4 mg of dexamethasone for reducing brain edema. Dexamethasone was to be continued in a dosage of 3 x 4 mg/d until early postoperative MRI (within 72 hours after the operation).

The investigational drug was administered to the patient in the presence of an investigator or a person designated by the investigator.

Statistical Analysis Plan

There were no dropouts so no imputation for missing data, no adjustments for co-variates, no sub-groups analysis, and no interim analysis.

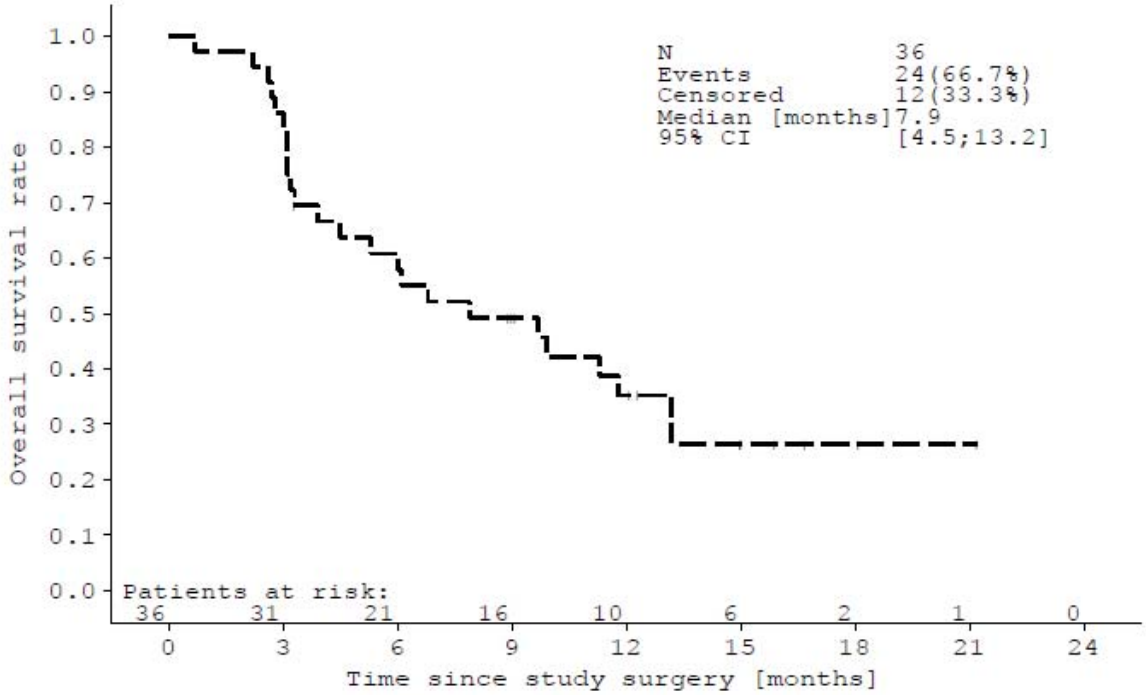
Efficacy Results - Primary Endpoint

The primary endpoint for this study is not the imaging endpoint the applicant has chosen for this NDA. This will be reviewed following this section. Briefly 78% patients had all the required 6 fluorescing biopsies taken but fewer than 50% had biopsies taken in "normal" appearing brain.

Efficacy Results - Secondary endpoints with explanation provided by applicant (Data not provided within the submission since it was only the PPV the applicant was using to demonstrate efficacy.)

1. Percentage of patients without residual tumor: 7/36 had no residual enhancement on post-operative MRI. According to central neuroradiological review, tumors could not be removed completely in the majority of patients, 25/36 with 41 sites of enhancement seen. Residual positions involved eloquent areas in 13/41 (31.7%) positions. In case of 24/41 (58.5%) positions revealing residual tumor, neuroradiological review did not find any relation to eloquent areas
2. Intraoperative evaluation of residual tumor by neurosurgeon: Using standard white light illumination, it was stated in 22/36 (61.1%) of patients that all tumor had been resected completely. Results did not change significantly if the same assessment was performed using the FL-mode of the microscope (21/36; 58.3% of patients without residual tumor), indicating that most of .residual tumor was recognized as such without the help of 5-ALA-visualisation. At least 5/25 positions (20%) were only detectable using the FL-mode of the microscope.
3. Overall Survival: Median overall survival was 7.9 months (95% CI: 4.5 – 13.2 months) for all patients in the Full-Analysis-Set. OS must be interpreted in light of follow-up therapies given. After study surgery, 2/36 patients (5.6%) underwent re-surgery, one patient was treated with radiotherapy and one patient received other therapies (Glivec/Litalir). Most of patients underwent some type of chemotherapy.

Figure 9 Kaplan-Meier Curve for Grade IV GBM in Study ALS-30



7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. **Primary Endpoints**

For the efficacy analysis, applicant has chosen PPV at the biopsy level to demonstrate performance. This was defined as Biopsy PPV = % FL histology Positive biopsies. For the phase 2 studies, this was a secondary endpoint; the primary endpoint was defined at the patient level. For the phase 3 trial, this was not an endpoint at but was analyzed post-hoc to determine the PPV. The standard for evaluation of the success of fluorescence was histology to show a correlation between the presence of fluorescence and tumor. Biopsy methodology differed in the three trials. All biopsied tissue was classified as Positive/Negative by Central Histology with and cellularity and tumor type classified as well.

ALS-28:

- Biopsy selection sites were determined after removal of tumor core and the necrotic tissue (debulking)
- Instructed to select 3 different sites with strong fluorescence to be measured

spectrometrically
- The surgeon also identified 3 areas of weak fluorescence to measure and sample
- If possible, 2 non-fluorescent areas were to measured and biopsied

ALS-30:
- Resection under WL
- Under WL areas were designated for biopsy as normal or abnormal by the surgeon. The fluorescence quality was then evaluated in these areas and biopsies taken. (Very Few Biopsies taken from non-fluorescing areas.)

ALS-3:
- Surgeons were allowed to use fluorescence as desired during the course of the resection.
- Geographic assignment of biopsy sites
    - Tumor core
    - Tumor margin
    - Distant
- Assessment of these areas as to the intensity of fluorescence

PPV as a stand-alone primary endpoint needs to be assessed in conjunction with at least one additional "visualization" endpoint. For our analysis alternative forms of PPV estimation and a complementary endpoint: Biopsy-level Fluorescence False Negative Rate (FNR-FL) were undertaken. The following are the definitions that informed our analyses:
- Biopsy Level:
    - BIOPSY PPV: % of FL biopsies that are Histology Positive (HP)
    - BIOPSY FNR-FL: % of Non-FL biopsies that are HP
- 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
- Subject-Level : this is the primary endpoint of studies ALS-28 and ALS-30
    - 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 11 Summary of PPV and FNR-FL for Each Study

STUDY ALS-3: PHASE 3 (170 Subjects) (Median #Biopsies = 3 ; Median # Fluorescent Biopsies = 2)					
PPV			FNR-FL		
BIOPSY (N=319)	WSUB (N=165)	SUB (N=165)	BIOPSY (N=160)	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		
BIOPSY (N=183)	WSUB (N=33)	SUB (N=33)	BIOPSY (N=112)	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		
BIOPSY (N=354)	WSUB (N=33)	SUB (N=33)	BIOPSY(N=16)	WSUB (N*)	SUB (N*)
97%	97%	78%	81%	N/A	N/A

When looking at the various ways in was analyzed, the PPV is near perfect for all three studies (96% to 98%). In this analysis fluorescence was considered together, that is, weak and strong areas were considered combined.

Another way to assess the visualization claim was to look at the fluorescence and tumor cellularity. In this analysis if any biopsy showed tumor it was considered positive.

Table 12 Summary of Cellularity and Fluorescence

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	2 (5%)	154 (35%)	266 (60%)	440
FL = STRONG	5 (1%)	46 (11%)	356 (87%)	407

Non-FL biopsies are still 80% positive for histology, with 66% of them (2 out of 3 Non-FL biopsies) with cellularity between 1% and 50%. For Weak-FL biopsies: about 1 in 3 have 1% to 50% cellularity and 3 in 5 have >50% Cellularity. For Strong FL: most histology has high cellularity (7 out of 8).

Furthermore, when looking at intensity of fluorescence and cellularity we find that there is also a fairly strong relationship between FL levels (None/Weak/Strong) and tumor type. Strong fluorescence corresponds to solid tumor while weak fluorescence has a histologic pattern of an infiltrative process and is usually in the margin of the tumor or in the resection cavity after debulking but Non-FL tissue is also likely to be cancerous – of the infiltrative type.

This exploratory analysis of the 5-ALA FL arm in ALS-03 study showed that fluorescence level could be predicted by region of biopsy and all three biopsied regions were largely histology positive.

In summary, PPV was very high, but 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.

For this NDA submission, the applicant did not provide secondary endpoints. The secondary endpoints in the original studies are discussed under each study in the previous sections.

7.1.2. Subpopulations

In these trials the final histopathology was not known until after surgery therefore there are patients who received the study drug but were excluded from efficacy analysis. An AI letter was sent to the sponsor and is pending at the time of this review.

Patients younger than 18 years were excluded from these trials. Since its approval it has been used off-label for suspected GBM in this population with similar results.[8]

7.1.3. Dose and Dose-Response

Not applicable

7.1.4. Onset, Duration, and Durability of Efficacy Effects

There is no therapeutic treatment effect. This product is a single use, diagnostic agent for which there is no expectation of durability or clinical benefit beyond the operating room.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

The reviewer does not recommend any postmarketing requirements. Based upon review of the literature and post-market safety report filed with the European agency in 2015 there are no drug safety signals that are not already known.

7.2.2. Other Relevant Benefits

Additional benefits of this product in this reviewer's assessment include:

- Strong correlation between fluorescence and presence of tumor allows for anaplastic foci to be identified in patients with low grade gliomas that have a high probability of malignant transformation. This allows for better histopathologic diagnosis to prevent

under-staging and under-treating.

- In patients with deep or otherwise unresectable tumors for whom tissue diagnosis is needed, use of this product may identify which areas of the tumor mass will yield the greatest likelihood of a histologic diagnosis reducing the number of passes needed to get a diagnosis and reducing the risk of sampling error and possible under-grading.
- Although not studied in these trials, there are published reports of the drug's use in the pediatric population who also can develop GBM's. The efficacy and safety parameters appear similar to the adult population.

7.3. Integrated Assessment of Effectiveness

Literature Review

The applicant provided 12 studies from the literature to support the PPV. Using the information in the studies they re-analyzed the data to determine only the PPV for 5-ALA. The methodology by which the papers were chosen required that: the publications use 5-ALA for glioma resection must have reported on biopsy-based PPV, the surgeon's assessment of fluorescence during resection, and resection completed under white light prior to fluorescence; or surgeon switched between the two. This resulted in 11 single-arm, prospective studies in which 2 required complete resection under WL followed by FL, 6 allowed surgeons to switch as desired, and 3 had no mention of how the fluorescence was used. Patients with primary or recurrent tumors were allowed and those studies where 5-ALA used in conjunction with other intra-operative assessment methods.

The following table summarizes the literature provided by the applicant as well as additional studies reviewed by this reviewer. Those highlighted were part of this submission.

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

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		
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

Highlighted papers were provided by the sponsor for support of PPV.

The results for PPV are consistent throughout all the studies and are nearly 100%. The NPV is highly variable from a low of 12% to a high of 90%. This demonstrates the fact that even in the absence of fluorescent activity tumor cells are present, which is consistent with the infiltrative nature of this disease. It is difficult to interpret sensitivity and specificity for this disease because of the ethical issues associated with mandating a biopsy of normal brain.

In this rare patient population, the product under review is the first to be used for intra-operative identification of GBM's. Based upon the review of the literature and the clinical data from the previously conducted European studies, the benefit of this product is demonstrated by the ability to be used intra-operatively in real-time to visualize these lethal tumors, improve resection rates when used in conjunction with other neurosurgical monitoring technologies, and will likely be more widely accessible for neurosurgeons and their patients than iMRI, which is only available at certain academic centers. Unfortunately, the study designs did not control for bias and true performance data such as sensitivity and specificity cannot be obtained for ethical reasons. To support the visualization claim, the positive predictive value was chosen for performance. In the original trials, ALS-28 and ALS-30, the biopsy level PPV was a secondary endpoint and in ALS-3, it was not an endpoint at all. The applicant has taken the available data from ALS-3 and done a post-hoc analysis to derive the PPV. The information is adequate to allow for a localization claim or as an adjunct to other intra-operative localization techniques.

8 Review of Safety

No drug safety issues were identified.

8.1. Safety Review Approach

There are no drug safety issues; however, because of the context in which the study drug is used there are procedure related outcomes that differed between the two arms in the single controlled study. The ability to remove more tumor can result in a greater neurological deficit post-operatively.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

This product is a single administration product. It is unlikely that a patient will receive a second dose except in the small number of cases where recurrent tumor is still amenable to surgical resection and the patient willing to undergo a second surgical procedure.

Table 13 Safety Population and Size

Clinical Trial Groups	New Drug (n=537)
Normal Volunteers (all male)	21
Controlled trials conducted for this indication	176
All other than controlled trials conducted for this indication	340
Controlled trials conducted for other indications	0

8.2.2. Relevant characteristics of the safety population:

The safety database consisted of the spectrum of patients one would find in the indicated population. Since patients with renal insufficiency and hepatic dysfunction were not included there is no data regarding the use of this drug in those populations. For patients with renal or hepatic co-morbidities, it would be the treating physician and practice of medicine to determine the individualized risk-benefit since GBM is a rapidly lethal disease.

8.2.3. Adequacy of the safety database:

The size and adequacy of the safety database for this orphan disease, single administration product is adequate. In addition, since the drug's approval in Europe in 2007, it has also been approved for use in South Korea, Taiwan, Japan, Israel, Australia, Hong Kong, Ukraine and Kuwait. As a result there have been an estimated 58,000 patient exposures without a new safety signal and no actions taken for a safety signal.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The applicant provided case report forms and narratives for the deaths in each trial but not for all the study subjects. The information on the CRF's was consistent across studies.

8.3.2. Categorization of Adverse Events

AEs were classified using standard terminology from the verbatim description according to MedDRA Coding Dictionary (Version 18.1). TEAEs were reported as mild, moderate, severe, life-threatening, or fatal and classified as short-term (within 1 week of surgery), mid-term (within the first 6 weeks) and long-term.

They can be divided into drug-related events and procedure-related events and were reported at the patient level. The most frequently reported AEs were those assigned to the CTC-category "Neurologic".

Under the heading of General Disorders there were 59 events listed. Although some could have been placed in a more specific body system category, only the cardiac arrest is of significance. This patient had underlying heart disease and did not receive surgery because the arrest occurred at the onset of the surgery.

8.3.3. Routine Clinical Tests

All patients were undergoing general anesthesia with routine patient monitoring. In addition, to assess the safety, the following tests were performed at the times specified in the tabular study schedule shown above for each study:

Blood pressure
Electrocardiogram (ECG)
Neurological examination (NIH score)
Karnofsky Performance Status
Blood count (leukocytes, erythrocytes, hemoglobin, hematocrit, platelets)
PTT
Sodium, potassium, creatinine, urea, gamma-GT, ALT (GPT), AST (GOT), amylase, glucose
Blood gas analysis
Pulse oximetry (intraoperative continuous, non-invasive pO_2 and $SatO_2$ monitoring)

8.4. Safety Results

Table 14 Summary of AE's across all Studies

	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

8.4.1. Deaths

There were a total of 284 deaths in all the trials. In all the studies 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 applicant provided CRF for 86 patients who died within 6 months of surgery. The most common events were thromboembolic such as pulmonary embolus or cerebral infarction. Cardiac issues contributed as well. During the follow-up phase deaths occurred as a result of progression of the tumor.

Table 15 Summary of Deaths within 6 months for All Studies

	ALS-8	ALS-28	ALS-30	ALS-3		ALS-32
				FL	WL	
Pulmonary Embolism/Vascular	0	1	1	8	4	2
Cardiac	0	0	0	3	4	1
Pneumonia	0	0	1	6	3	1
Infections	0	0	0	1	3	3
Progression of Disease	0	0	9	1	2	20

Herniation Brain	0	0	0	0	1	2
Bleeding	0	0	0	0	1	0
Unknown			1			6

Reviewer Comment: There were a higher number of embolic events in the treated group overall, however when looked at more closely, only four occurred in the immediate post-operative phase, the remainder occurred after 30 days. For these patients, the risk of thromboembolic events is about 30%. Malignancy, limited mobility, and age are known risk factors for these events.

8.4.2. 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. All eventually resolved.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

No patients were discontinued or dropped due to Adverse Events.

8.4.4. Significant Adverse Events

Table 16 AE Summary

System Organ Class	ALS-8 (n=7)	ALS-28 (n=26)	ALS-30 (n=40)	ALS-3 N=201)	ALS-32 (n=242)	Pooled (n=242)
Nervous System*	58	48	29	333	126	594
Infections	7	4	3	50	23	87
Injury, Procedural Complications	1	1	1	19	34	56
Respiratory	11	2	0	23	3	39
Vascular Disorders	8	4	0	23	15	50
Cardiac Disorders	7	0	0	13	0	20
Gastrointestinal	6	10	3	22	7	49
Skin and Subcutaneous	4	3	0	17	5	29
Immune system/Allergy (none to the study drug)	3	0	0	3	1	7

*these are discussed separately elsewhere in this review

There were 59 AE's classified as general disorders. One was listed as unsteady gait which could have been coded under nervous system. There were five wound complications not well described, six patients with fluid accumulation at the surgical site, and 20 incidences of post-operative fever.

Reviewer Comment: The spectrum of AE's seen reflect the nature of the disease, the surgical procedure, and patient population.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Table 17 Summary of TEAE's All Studies provided by the Applicant

	Study N (%)						
Number of Patients with Any:	MC-ALS.8 (N = 7)	MC-ALS.28 (N = 36)	MC-ALS.30 (N = 40)	MC-ALS.3 WL Control (N = 173)	MC-ALS.3 (N = 201)	MC-ALS.32 (N = 243)	Pooled Studies (N = 527)
Treatment-emergent Adverse Event (TEAE)	7 (100%)	27 (75.0%)	22 (55.0%)	111 (64.2%)	135 (67.2%)	126 (51.9%)	317 (60.2%)
Total Events	37	90	48	275	348	279	802
Drug-related TEAE	2 (28.6%)	6 (16.7%)	0 (0%)	0 (0%)	7 (3.5%)	3 (1.2%)	18 (3.4%)
Total Events	4	6	0	0	8	5	23
Severity							
Mild TEAE	0 (0%)	1 (2.8%)	2 (5.0%)	28 (16.2%)	33 (16.4%)	30 (12.3%)	66 (12.5%)
Moderate TEAE	5 (71.4%)	10 (27.8%)	15 (37.5%)	33 (19.1%)	26 (12.9%)	50 (20.6%)	106 (20.1%)
Severe TEAE	2 (28.6%)	14 (38.9%)	5 (12.5%)	28 (16.2)	45 (22.4%)	34 (14.0%)	100 (19.0%)
Life-Threatening TEAE	0 (0%)	0 (0%)	0 (0%)	9 (5.2%)	13 (6.5%)	12 (4.9%)	25 (4.7%)
Fatal TEAE	0 (0%)	2 (5.6%)	0 (0%)	13 (7.5)	18 (9.0%)	0 (0%)	20 (3.8%)
Serious Adverse Event	1 (14.3%)	8 (22.2%)	4 (10.0%)	43 (24.9%)	68 (33.8%)	49 (20.2%)	130 (24.7%)
Adverse Event Leading to Discontinuation	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Adverse Event Leading to Death	0 (0%)	2 (5.6%)	0 (0%)	13 (7.5%)	18 (9.0%)	5 (2.1%)	25 (4.7%)

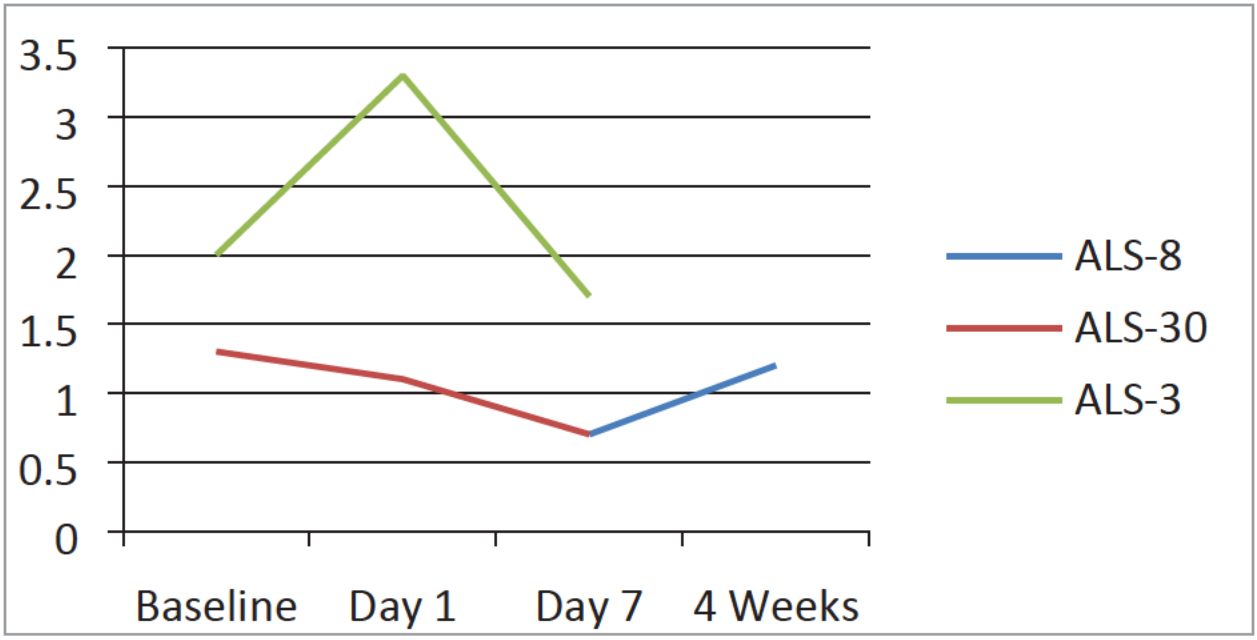
- Drug related events were few.
- There were no AE's leading to discontinuation
- Most TEAE's (42%) were neurologic in nature occurring within the first week after surgery and due to the surgical procedure.
- Pyrexia, hypertension, nausea and vomiting also occurred in >1% during the first week which were attributed to the drug effects.

8.4.6. Laboratory Findings

With the world-wide experience with this drug a transient elevation in liver function test is known to occur. The applicant provided data and identified the following transient elevation in bilirubin, alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT). Patients experienced a worsening of ≥ 2 Common Toxicity Criteria (CTC) grades in alanine ALT and GGT

(15.8% and 11.6%, respectively) within the first week after surgery. At 6 weeks, ALT remained elevated in 2.9% of patients, and GGT was elevated in 7.5% of patients. There were no cases of liver failure observed. An additional review was done for bilirubin and the following graph illustrates the results.

Figure 10 Bilirubin Values over Time (ALS-8, ALS-30, and ALS-3)



*highest value charted

A retrospective review by Chung and Elijamel[9] evaluated risk factors for elevated liver enzymes or hypotension. The authors reported that changes in liver enzymes were transient and mild consistent with this application.

8.4.7. Vital Signs

Since patients were undergoing surgery, they were continuously monitored by anesthesiologists. There were patients with transient elevation or decreases in their blood pressure. The paper by Chung and Elijamel[50] found that hypotension was more likely to occur if patients were on anti-hypertensive medications.

8.4.8. Electrocardiograms (ECGs)

ECG's were collected in studies ALS-20, ALS-8 and ALS-28 but the times varied relative to the surgery and could not be pooled per applicant. ECG's were also collected in healthy human volunteers (n=21) in ALS-20. None of the ECG parameters changed consistently from pre- to final check in the healthy volunteers.

Study ALS-8 was the only clinical study to specifically look at QT prolongation. Recordings were taken at 30-, 60-, 120-minutes after administration, and Days 1, 2 and 7 post-operative. The changes noted were non-specific in nature and required no treatment.

For ALS-28 ECG monitoring was the same as in ALS-8. Monitoring during the perioperative phase was done by anesthesiology and was immediately corrected. Specific adverse reactions that could be attributed to administration of the study drug, except for a single patient who received antihypertensive medication for known arterial hypertension and in whom an episode of intraoperative hypotension occurred, no obvious deviations were registered in this study concerning these parameters, including ECG.

8.4.9. QT

In a pre-NDA meeting held in June 2015, FDA stated that "the available QT data may be adequate". In studies MC-ALS.28/GLI and MC-ALS.8-I/GLI, ECGs were taken 30, 60, and 120 minutes following administration of Gliolan. Electrocardiogram (ECG) data is available from studies MC-ALS.8 only. The following table summarizes the abnormal QT data.

Table 18 QT abnormalities study ALS-8

	No. of patients	Gender	No. of Patients
30 minutes	3	Male	2
		Female	1
60 minutes	5	Male	4
		Female	1
120 minutes	4	Male	2
		Female	2
Post-operative	1	Male	1
		Female	0
Day 2	1	Male	1
		Female	0
Day 7	1	Male	1
		Female	0

All were single readings at a single point in time. There were no patients with sustained changes or multiple abnormal values. As this product will only be given a single time and all patients will be undergoing surgery with intensive intra-operative monitoring these findings raise no safety concerns.

The applicant provided the following table with information from all studies.

Table 38. Incidence of TEAE of Special Interest by Preferred Term—Torsade de pointes/QT prolongation

SMQ: Torsade de pointes/QT prolongation Preferred Term	Study N (%)					
	MC-ALS.8	MC-ALS.28	MC-ALS.30	MC-ALS.3	MC-ALS.32	Pooled Studies
Short Term	(N = 7)	(N = 36)	(N = 40)	(N = 201)	(N = 243)	(N = 527)
Overall	0 (0%)	1 (2.8%)	0 (0%)	2 (1.0%)	0 (0%)	3 (0.6%)
Syncope	0 (0%)	1 (2.8%)	0 (0%)	0 (0%)	0 (0%)	1 (0.2%)
Cardiac arrest	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)	0 (0%)	1 (0.2%)
Ventricular fibrillation	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)	0 (0%)	1 (0.2%)
Mid Term	(N = 7)	(N = 35)	(N = 39)	(N = 198)	(N = 241)	(N = 520)
Overall	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)	1 (0.2%)
Syncope	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)	1 (0.2%)
Long Term	(N = 0)	(N = 0)	(N = 36)	(N = 186)	(N = 231)	(N = 453)
Overall	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)	0 (0%)	1 (0.2%)
Cardiac death	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)	0 (0%)	1 (0.2%)

Patients reporting a particular AE (preferred term) more than once are counted only once by preferred term and system organ class.

The applicant also stated that the post-marketing world-wide data base was queried and there were no cardiac events associated with QT prolongation.

8.4.10. Immunogenicity

Not applicable.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Neurologic Events

As would be expected in this population, the serious adverse events were procedure related. Since there is a possibility that with greater resection there would be a worsening of neurologic deficits, I have concentrated on those findings. They are summarized below for all the 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	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

Of note is that in the controlled study, ALS-3, there were more AE's affecting vision. This may be due to the proximity of the tumor to those areas of the brain, as there were twice as many tumors near the optic region in the FL arm. There are also a greater number of aphasic events in the treated arm which cannot be easily explained by tumor location.

The neurosurgeons expect that 30-60% of patients will experience post-op seizures, so patients will receive anti-epileptics in the post-operative period. Della Puppa et al[10] found that 70% of patients with an immediate post-operative neurologic deficit recovered to baseline and only 3% had a severe new neurological deficit. He concluded that the high early morbidity seen with aggressive resection was transient in the majority of patients.

8.5.2. **Photosensitivity**

5-ALA is a fluorophore and activated by exposure to certain light frequencies. It is not unusual that effects from exposure to sunlight and ambient lighting could result in photosensitivity issues. These are manifested in the skin. In the trials presented this reported in 2 patients for study ALS-3, one in each arm. In a summary of the post-marketing reports, this is reported twice. In all cases the severity was classified as mild. This risk can be mitigated by keeping the patient in a darkened environment for 24-48 hours post-operative and minimizing their exposure to light.

8.6. Safety Analyses by Demographic Subgroups

Age, gender and KPS score are known prognostic factors. When these parameters were looked at there were no differences seen based on age, gender or KPS.

8.7. Specific Safety Studies/Clinical Trials

Not applicable.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Not available as this is a lethal disease with limited survival expectations and is given as a single dose.

8.8.2. Human Reproduction and Pregnancy

There were no exposures in pregnancy or lactating women.

8.8.3. Pediatrics and Assessment of Effects on Growth

The drug has been used off-label in Europe for suspected pediatric GBM. Stummer et al found the safety and efficacy to be similar to the adult population studies. There is no information on the effect of 5-ALA on growth.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

This is a single use drug given prior to surgery so the risks for drug abuse potential, withdrawal and redound do not apply. Only two cases of accidental 5-ALA overdose were reported in the European PSUR from 2015 resulting in mild redness of the face.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

No new or unexpected issues seen world-wide.

8.9.2. Expectations on Safety in the Postmarket Setting

This drug has been in use for 10 years with no safety signals identified. The adverse reactions most 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. It has also been used off-label in the pediatric population without safety signal as well.

8.10. Additional Safety Issues From Other Disciplines

No additional safety issues.

8.11. Integrated Assessment of Safety

5-ALA is a safe drug when used in the prescribed manner for this population. Physicians should be aware of the potential for transient elevations in LFT's and monitor patients accordingly. The known photosensitivity reactions can be mitigated by limiting the patient exposure to sunlight or room lights for 48 hours. As these patients are usually in the ICU for this time period, this is easily managed.

The potential for worsening neurologic effect as a result of surgery is a factor that all neurosurgeons must take in to account if using this drug. However, every time a patient undergoes brain tumor resection, surgical judgement is critical to achieving safe maximal resection. It is unlikely that the surgeon will compromise outcome by resecting tumor in eloquent areas even if it is fluorescent.

9 Advisory Committee Meeting and Other External Consultations

An Advisory Panel was held on May 10, 2017. The committee voted unanimously for approval of 5-ALA (Gleolan) for a visualization claim.

10 Labeling Recommendations

10.1. Prescribing Information

The following changes have been discussed in labeling meetings. The final comments have not been sent to the sponsor.

- **Indications and usage**
  - I have proposed the following modification of the applicant's indication to reflect the data reviewed and by consistent with the European label:
    "An imagining agent indicated as an adjunct to other neurosurgical tools, to visualize WHO grades III and IV gliomas intra-operatively during glioma surgery"
- **Dosage and Administration**
  - Added language regarding the modifications required to the operating

microscopes to allow visualization of the fluorophore as requested by CDRH

- **Section 5 Warnings and Precautions**
  - Risk of Phototoxic Reaction mitigated by reducing exposure to light
  - Risk of Misinterpretation to alert neurosurgeons that errors may occur in interpreting the presence/absence of tumor in fluorescent and non-fluorescent areas as the absence of fluorescence does not rule out residual tumor

10.2. Patient Labeling

Not applicable

10.3. Nonprescription Labeling

Not applicable

11 Risk Evaluation and Mitigation Strategies (REMS)

11.1. Safety Issue(s) that Warrant Consideration of a REMS

The safety concern relates to the surgical procedure and not issues identified with the drug.

11.2. Conditions of Use to Address Safety Issue(s)

There are some technical aspects to successful use of this drug. The sponsor has been required in Europe to provide training and certification/re-certification for neurosurgeons which address these concerns. They have requested that the US approval contain a similar requirement.

11.3. Recommendations on REMS

Given the favorable safety profile of this drug in the given population, there are no additional risk management strategies required beyond the recommended labeling. Therefore, the subsequent subsections are not applicable for this review and have been omitted.

12 Postmarketing Requirements and Commitments

None recommended.

13 Appendices

13.1. References

13.2. Financial Disclosure

NX Development Corporation (NXDC), the applicant of this New Drug Application (NDA) 20863 submitting covered clinical studies sponsored by a firm or party other than the applicant. They state that "*No clinical investigator in the covered clinical studies was an employee, full or part time, of the study Sponsor (medac GmbH, Germany) during study conduct*".

Covered Clinical Study (Name and/or Number): MC-ALS.28/GLI, MC-ALS-.30/GLI, MC-ALS.3/GLI

Was a list of clinical investigators provided:	Yes x☐	No ☐ (Request list from Applicant)
Total number of investigators identified: _____		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): _____		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be		

influenced by the outcome of the study: N Significant payments of other sorts: N Proprietary interest in the product tested held by investigator: N Significant equity interest held by investigator in S Sponsor of covered study: N		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes x☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes x☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 2		
Is an attachment provided with the reason:	Yes x☐	No ☐ (Request explanation from Applicant)

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

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/s/

BETSY BALLARD
06/01/2017

NUSHIN F TODD
06/01/2017

M E M O R A N D U M

Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

FROM:	Diana Bradford, Medical Review Officer, DOP2
THROUGH:	Suzanne Demko, Team Leader, DOP2
THROUGH:	Patricia Keegan, Division Director, DOP2
SUBMISSION #:	NDA 208630
REQUESTED BY:	CDER/DMIP
PRODUCT:	Gliolan
SPONSOR:	NX Development Corp
DATE OF REQUEST:	March 31, 2017
REQUESTED COMPLETION:	April 12, 2017
DATE COMPLETED:	April 4, 2017

On March 31, 2017, the Division of Medical Imaging Products (DMIP) within the Office of Drug Evaluation IV (ODEIV) requested a consult from the Division of Oncology Products 2 (DOP2) regarding Gliolan, an intra-operative imaging agent proposed for use in patients with malignant glioma. DMIP specifically requests DOP2 to assess whether progression-free survival (PFS) is adequate as an efficacy outcome for assessing the clinical benefit of Gliolan as an intra-operative imaging agent to facilitate the real time detection and visualization of malignant tissue in patients undergoing surgery for glioma. NX Development Corp (NXDC) submitted an original New Drug Application (NDA) 208630 for Gliolan® (5-aminolevulinic acid hydrochloride [5-ALA HCl] for oral solution) for use as an imaging agent to facilitate the real time detection and visualization of malignant tissue during glioma surgery.

Background

The World Health Organization (WHO) grading system is a widely accepted scale used to categorize tumors; high grade glioma includes anaplastic astrocytoma (AA, WHO grade III) and glioblastoma (GBM, WHO grade IV). With optimal upfront therapy including maximal safe surgical resection, radiation therapy (RT) and chemotherapy, the median overall survival (OS) is 3-5 years for AA, and < 15 months for GBM.

Maximal safe resection for brain tumors is the accepted standard of care. A prospective trial conducted by Vuorinen *et al* randomized 30 elderly patients (> age 65) with suspected malignant glioma to stereotactic biopsy or open craniotomy and resection. (Vuorinen V, 2003) The median overall survival (OS) in the craniotomy vs. biopsy groups was 171and 85 days, respectively. Available retrospective data consistently indicate progression free survival (PFS) and OS are correlated with extent of resection (EOR); however, in these studies most assessments are based on the surgeons' determinations of degree of resection. (McGirt MJ, 2009) (Hess KR, 1999) (Keles GE, 2006) (Lacroix M, 2001) Despite the lack of randomized controlled trials, the current consensus among neurosurgeons and neuro-oncologists is that optimal treatment of malignant glioma should include maximal safe resection and that increasing the EOR correlates with improved patient outcomes.

Gliolan

Gliolan contains the active substance 5-aminolevulinic acid HCl (5-ALA) a prodrug that is metabolized intracellularly to form a fluorescent molecule protoporphyrin IX (PPIX). Administration of 5-ALA leads to preferential accumulation of PPIX in tumor cells and following exposure to blue light (λ= 400 - 410 nm) PPIX emits a red-violet fluorescence, distinguishing tumor cells to guide surgical resection. According to information in the EMA EPAR, this phenomenon appears to be restricted to high grade tumors; conversely, in low-grade tumors (WHO grade I/II, medulloblastoma, oligodendroglioma) fluorescence is not observed after administration of 5-ALA. Explanations for higher 5-ALA uptake in malignant cells include a disrupted blood-brain barrier, increased neo-vascularization, and overexpression of membrane transporters.

Gliolan was approved in 2007 by the EMA and in 2013 by the Australian Therapeutic Goods Administration (TGA). In Europe, the indication is for visualization of malignant tissue during surgery for malignant glioma (WHO grade III and IV), while in Australia the indication is limited to patients with GBM. Approval by both regulatory agencies was based primarily on data from a multicenter trial (MC-ALS.3/GLI) that randomized 415 patients with radiographic evidence of a single focus of suspected malignant glioma amenable to gross total resection (GTR) of contrast enhancing tumor, to either fluorescence-guided resection after administration of 20 mg/kg orally of 5-ALA HCl (n=205) or conventional white light surgery (n=208). The primary endpoints were rate of GTRof contrast-enhancing tumor on post-operative MRI (within 72 hours after surgery), and 6 month progression-free survival rates (PFS6) after surgery. Secondary endpoints included PFS at 9, 12, 15, and 18 months after surgery, volume of residual tumor, OS, toxicity. Radiological progression was defined as the occurrence of a new tumor lesion or an increase in volume of residual tumor of >25% as evaluated by independent radiologists blinded to treatment. PFS6 was defined as the rate of patients who were alive at the 6 month visit and did not have evidence of radiological progression.

Sixty-three percent (63.6%) of all patients in the fluorescence-guided (FL) group and 37.6% of all patients in the control group (white light, WL) did not show residual tumor on early postoperative MRI ($p<0.0001$). The PFS6 rates were 20.5% in the FL-group and 11.0% in the WL-group ($p= 0.0152$). NXDC states that logistic regression models were fitted including covariates of age group, performance score, endangerment of eloquent areas and study center, but did not include administration of chemotherapy.

Most patients received post-operative radiotherapy, including 90.9% of the FL-group and 93.6% of the WL-group. The protocol did not include concomitant chemotherapy or radiosensitizing agents, and no adjuvant therapy was recommended until the time of progression. However, some patients did receive chemotherapy before radiological progression, including 12.5% of patients in the FL-group and 13.3% of patients in the control group; the most common reason for chemotherapy administration was patient request. The type of chemotherapy was not specified in the protocol, and the most common type of chemotherapy administered in these patients was temozolomide. It is not clear from the information provided in the consult how administration of chemotherapy was addressed in the PFS6 model. Before radiological progression, three patients in the control arm had a second resection; none in the FL-group underwent repeat surgical procedure. Time to re-intervention was prolonged in patients who underwent fluorescence-guided resection (9 vs 7.1 months; $p = 0.09$). More patients in the control group underwent a second operation (30 vs 39%; $p = 0.03$).

Brief regulatory history (FDA)

In 2011, the sponsor (NX PharmGen) had a Type B, pre-IND meeting with FDA to discuss the clinical development plans for Gliolan and a proposed study, "RTOG Phase III Randomized Controlled Multicenter Trial of Fluorescence-Guided Surgery with 5-Aminolevulinic Acid for Resection of Newly Diagnosed Glioblastoma." FDA expressed concerns with using a radiological surrogate endpoint as a primary efficacy endpoint, and emphasized that clinical benefits need to be demonstrated. On September 22, 2014 the sponsor (NX Development Corporation (NXDC)) had a Type C meeting with FDA to discuss plans for the submission of an NDA for Gliolan. The proposed indication was "As an imaging agent to facilitate the real time detection and visualization of malignant tissue during glioma surgery." In addition to the existing data from Study MC-ALS.3/GLI, NXDC proposed to provide data from two studies: Study MC-ALS.28/GLI and study MC-ALS.30/GLI, both designed to determine the positive predictive value of Gliolan induced tissue fluorescence for tumor cell detection in patients with newly diagnosed or recurrent malignant glioma. FDA agreed with the plan to provide data on the performance of Gliolan for distinguishing between normal and malignant tissue by using the histopathology from brain biopsies as a truth standard; however, FDA again cautioned that the assessment of extent of tumor resection based on postoperative imaging is not an adequate efficacy endpoint. FDA recommended NXDC provide data that demonstrate the use of Gliolan for enhancing delineation of tumor resection margins in an adequately controlled study and proposed that patients with WHO grade 3 and 4 gliomas undergo maximal tumor resection under white light only, followed by additional Gliolan-aided resection. Documentation of fluorescence in the resection margin would be performed and biopsies would be obtained for verification of tumor status.

DOP2 was consulted at this time. In a consult dated October 14, 2014, DMIP posed the following question:

> *Gliolan is a fluorescent optical imaging agent proposed for use intra-operatively in patients with Grade III and IV gliomas as an aid in the visualization of tumor margins. Randomized trials have failed to show improved overall survival in patients undergoing Gliolan fluorescence-aided tumor resection compared to standard white light resection. No new randomized trials with a survival outcome are planned. Please comment on whether within*

this intended patient population there is a subgroup for whom an improvement in tumor resection margins could be of clinical value (see attached 2014 meeting comments). Gliolan was authorized for use in the EU (2007, see attached) based on evidence of lower brain tumor volume at postoperative MRI and improvement in PFS. We do not find that evidence to be persuasive (see attached 2011 meeting minutes).
In the consult, DOP2 suggested that the proposed evaluation of post-operative residual tumor volume was prone to inter-observer variability and observer bias; DOP2 suggested that intraoperative MRI could be used to assess for the presence of residual disease. DOP2 further commented that patients who are not identified as candidates for gross total resection (GTR) may derive the most benefit from an improved extent of resection (EOR). DOP2 suggested consideration of the evaluation of the use of Gliolan in low grade gliomas, as these tumors may be non-enhancing with more visually obscure borders.

In Written Responses to a pre-NDA meeting request dated April 18, 2016, FDA expressed concerns about the primary efficacy endpoint of positive predictive value from Studies MC-ALS.28/GLI, MC-ALS.30/GLI, and MC-ALS.3/GLI. On December 5, 2016, NXDC submitted NDA 208630 for Gliolan with a primary efficacy endpoint of positive predictive value of tissue florescence at the biopsy level.

Gliolan received Orphan Drug Designation by U.S. Food and Drug Administration (FDA) on January 15, 2013 for the visualization of malignant tissue during surgery for malignant glioma. FDA also granted Fast Track designation on December 21, 2015 to the development program by NXDC for the investigation of Gliolan for use as an imaging agent to facilitate the real time detection and visualization of malignant tissue during glioma surgery.

Six clinical studies are included in the NDA submission, all conducted in Germany and not conducted under a United States Investigational New Drug Application (IND). The studies are as follows:

Study MC-ALS.20/BV was a single-dose, single-center, randomized phase I study in healthy male subjects. Study MC-ALS8.I/GLI was a single-dose, prospective, single-center, double-blind, randomized Phase 1/2 study.

Study MC-ALS.28/GLI was a Prospective, multicenter, single-arm, nonrandomized, rater-blinded, uncontrolled Phase 2 study of 39 patients designed to determine the positive predictive value of tissue fluorescence and safety of 5-ALA .

Study MC-ALS.30/GLI was a prospective, multicenter, single-arm, nonrandomized, rater-blinded uncontrolled Phase 2 study of 40 patients with progressive or recurrent malignant gliomas, with the objective of determining the positive predictive value of tissue fluorescence and safety of 5-ALA.

Study MC-ALS.3/GLI (discussed above) was a prospective, multicenter, randomized, parallel-group, group-sequential, rater-blinded, 2-arm, controlled Phase 3 study of 415 patients with an objective of determining the efficacy and safety of fluorescence-guided resection of malignant gliomas with 5-ALA compared to conventional resection and to assess the clinical utility of this method. Patients were 18-72 years old with an MRI consistent with a diagnosis of malignant glioma that was contrast-enhancing. The primary

endpoints were percentage of patients without definite residual contrast-enhancing tumor in the early post-operative control MRI, and PFS-6.

Study MC-ALS.32/GLI was a prospective, multicenter, single-arm, nonrandomized, open-label, uncontrolled Phase 3 study of 245 patients with malignant glioma, which sought to determine the incidence of adverse events after fluorescence-guided resection of malignant gliomas using 5-ALA.

Reviewer Comments

As discussed above, the current consensus among neurosurgeons and neuro-oncologists is that optimal treatment of malignant glioma should include maximal safe resection and that increasing the EOR correlates with improved patient outcomes. However, radiologic assessment of high grade gliomas, and thus assessments of progression based on radiologic measurements, is subject to inter-observer variability. (Provenzale JM, July 2012) Progression-free survival thus has limitations as an endpoint in the assessment of clinical benefit for patients with high-grade gliomas, except where the magnitude of the treatment effect as detected by an independent observer or group of observers is so large that it is unlikely to be due to inter-observer variability alone and is likely to be considered direct evidence of clinical benefit. Overall survival is the preferred endpoint to demonstrate a clinical benefit in patients with high grade gliomas.

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04/10/2017