A randomized, blinded study of fluorescence detection of pediatric primary central nervous system tumors in subjects receiving tozuleristide and imaged with the Canvas System

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CONFIDENTIALITY STATEMENT

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Revision History

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Version 5.0	

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PROTOCOL SIGNATURE PAGE

Protocol No.: BB-006 (PNOC012) Amendment 5.0 Version Date: 28 October 2021

Investigator Statement

I have read and understood the protocol entitled: "A randomized, blinded study of fluorescence detection of pediatric primary central nervous system tumors in subjects receiving tozuleristide and imaged with the Canvas System"

I will conduct this study in accordance with this protocol (subject to amendments) and the current principles of Good Clinical Practice (GCP), International Conference on Harmonization (ICH E6R2) guidelines and any additional local guidelines as applicable. Any changes in procedure will only be made if necessary to protect the safety, rights or welfare of subjects. I will make all reasonable efforts to complete the study within the time designated. I agree to disclose the financial interests of all investigators or sub-investigators who are directly involved in the treatment or evaluation of research subjects.

This study will support an FDA submission and is subject to compliance with 21 CFR 312.60 for the drug component and ISO 14155:2011, 21 CFR 812.100 and 812.110 for the device component in addition to 21 CFR 11, 50, 54 and 56.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Blaze Bioscience. I will provide all study personnel under my supervision with copies of the protocol and access to all information provided by Blaze Bioscience. I will discuss this material with them to ensure that they are fully informed about the investigational product(s) and the study

Principal Investigator's Name (Printed)	Signature
	Date (dd mmm yyyy)

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ABSTRACT

Title	A randomized, blinded study of fluorescence detection of pediatric primary central nervous system tumors in subjects receiving tozuleristide and imaged with the Canvas System
Subject population	Subjects >1 month and ≤30 years of age at the time of study enrollment who have an MRI obtained within 30 days of study enrollment documenting a measurable lesion consistent with a pediatric primary CNS tumor for which maximal safe resection is indicated.
Rationale for Study	There is an urgent unmet need for a tumor-targeted imaging agent to enable real-time intraoperative distinction between malignant and normal tissue to improve neurosurgical outcomes, [redacted]
Primary Objective	The primary objectives of this study in subjects undergoing neurosurgical resection of pediatric primary central nervous system (CNS) tumors are: • To compare the sensitivity of tozuleristide and the Canvas near infrared (NIR) imaging system fluorescence to the sensitivity of surgical designation in equivocal tissue in situ; • To compare the specificity of tozuleristide and the Canvas system fluorescence to the specificity of surgical designation in equivocal tissue in situ; • To evaluate imaging efficacy as measured by sensitivity of tozuleristide and the Canvas system in facilitating intraoperative fluorescence detection and visualization of tumor in equivocal tissue in situ; • To evaluate imaging efficacy as measured by specificity of tozuleristide and the Canvas system in facilitating intraoperative fluorescence detection and visualization of tumor in equivocal tissue in situ.
Secondary/Exploratory Objectives	The secondary objectives of this study are: • To evaluate the safety of tozuleristide administration and Canvas NIR imaging system during surgical resection of pediatric primary CNS tumors • [redacted]

	[redacted] The exploratory objectives of this study will evaluate the: • [redacted] [redacted] [redacted]
Study Design	Randomized, blinded (central pathology, central fluorescence assessment and central radiology), multi-center study of a single dose of tozuleristide in subjects with pediatric primary CNS tumors; intraoperative imaging will be performed with the Canvas system. Two Arms (randomized 1:10): • Arm 1 (no drug treatment): ~9% of subjects Subject not injected with tozuleristide and undergoes standard of care neurosurgery • Arm 2 (tozuleristide treated): ~91% of subjects Subject injected with tozuleristide and undergoes standard of care neurosurgery During the surgical procedure, and once the tumor has been accessed, the Canvas system, which is attached to the surgical microscope, will be used to capture and display intraoperative *in situ* images (white light and fluorescence) of the region from which surgical specimens for biopsy or excision will be collected. All clinical decision-making regarding tissue resection will be made based on the routine neurosurgical practices, and tissue resection will take place under normal light conditions in line with best clinical practices. In addition to primary tumor biopsy, regions of equivocal nature (uncertain if tumor or not tumor) will be identified before fluorescence in the operating room is determined. Each clinical site will have an imaging operator who is not operating nor involved with patient surgical management. The imaging operator will ensure white light and fluorescent images are captured and will assess and document fluorescence status (none, weak, or strong) by looking at the Canvas monitor. The operating surgeon will assign presumed status of equivocal tissue (tumor/not tumor) and indicate the region to be biopsied and imaged by pointing at it with an instrument under the microscope. [redacted]

[redacted]

Tozuleristide and the Canvas system are intended as an aid to surgical decision-making. As such, when a region of interest in the brain/spine is noted to be fluorescent, it is always the surgeon's decision whether to biopsy/resect if safe to do so.

A 1:10 randomization scheme will be used to help reduce selection bias, and aid in the integrity of the blinded pathology, [redacted] and radiology assessments. Subjects will be randomly assigned to either Arm 1 (no tozuleristide treatment) or Arm 2 (tozuleristide treated) after enrollment. [redacted] Fluorescence assessment by the imaging operators will be used in the primary efficacy analyses.

Subjects who are randomized to Arm 1 or Arm 2 and need to undergo an additional surgery for their brain tumor will be eligible to receive tozuleristide without being subject to randomization. Subjects must meet all study eligibility requirements and re-consent for study prior to re-enrollment for open-label treatment with tozuleristide (re-treatment).

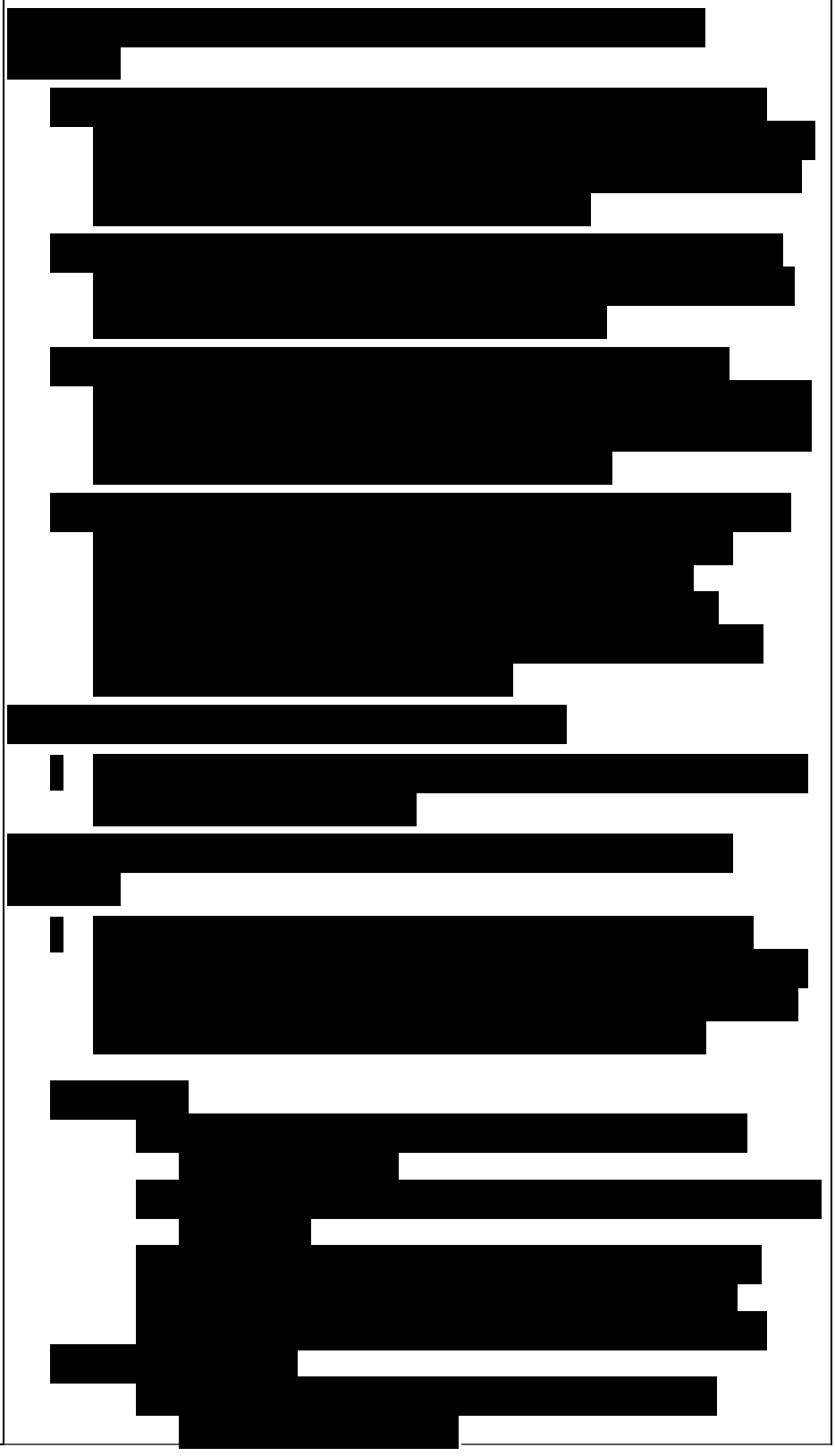
The pathology assessment of tissue as tumor or not tumor, for both arms, will be done by a centralized and independent panel of pathologists without knowledge of fluorescence status or treatment arm (blinded pathology).

Post-operative centralized and independent MR image assessment [redacted], for both arms, will be done without knowledge of fluorescence status, treatment assignment, or surgical assessment (blinded radiology).

	[redacted]
Number of Subjects	Approximately 114 subjects are planned.
Duration of Therapy	For subjects in Arm 2, tozuleristide will be administered as a single intravenous (IV) bolus dose at least one hour and no more than 36 hours before planned start time of surgery.
Duration of Follow up	Three months post-surgery
Duration of study	Approximately 52 months
Study Drug(s)	[redacted]
Safety Assessments	All adverse events (AEs) and SAEs for up to three months after surgery will be recorded and graded for evaluable subjects according to the National Cancer Institute's Common Terminology for Adverse Events (NCI CTCAE, Version 5.0) along with attribution of relatedness to tozuleristide and/or Canvas system and neurosurgery (related vs. unrelated). After the Day 8 visit, all subjects will be followed by chart review and/or telephone contact monthly for three months, or until an off-study criterion is met, to collect survival, toxicity assessment, and disease status information. Any subject receiving additional therapy for their CNS tumor, including chemotherapy and/or radiation therapy within three months of surgery will be considered off study for safety observations at the time of starting additional therapy. Safety data in these subjects will be included up to the time the subject begins additional tumor-directed therapy. Quality of life assessments will be collected in all subjects through three months post-surgery.
Primary endpoints	Primary efficacy endpoints are: 1. Ratio of sensitivity of tozuleristide fluorescence in equivocal tissue biopsies from subjects with fluorescence-positive tumors compared to the sensitivity of surgical designation from the same biopsies under white light conditions 2. Ratio of specificity of tozuleristide fluorescence in equivocal tissue biopsies from subjects with fluorescence-positive tumors compared to the specificity of surgical designation from the same biopsies under white light conditions

	3. Sensitivity of tozuleristide fluorescence to detect tumor in equivocal tissue biopsies from subjects with fluorescence-positive tumor 4. Specificity of tozuleristide fluorescence to detect tumor in equivocal tissue biopsies from subjects with fluorescence-positive tumor Tozuleristide fluorescence is determined by the imaging operator fluorescence assessment. [redacted]
Secondary endpoints	Secondary efficacy endpoints are: 1. [redacted] 2. [redacted] Secondary endpoints related to the safety objective: 1. All reported adverse events (AEs) will be graded according to the National Cancer Institute's Common. Terminology for Adverse Events (NCI CTCAE, Version 5.0) 2. SAEs 3. AE attribution of relatedness to tozuleristide and/or Canvas system (related vs. unrelated).

4. Laboratory parameters
5. ECG parameters
6. Vital signs



	[redacted]
Other study endpoints	[redacted]
Sample size determination	The sample size is based on the four co-primary endpoints for the tozuleristide arm (Arm 2). The sample size for the ratio of sensitivity of tozuleristide fluorescence in biopsies compared to the sensitivity of surgical designation from the same biopsies under white light conditions is based on the equivocal tissue biopsies from the subjects with fluorescence-positive tumor assessed for fluorescence and standard of care/white light conditions. [redacted]

	[redacted] The sample size for sensitivity and specificity of tozuleristide fluorescence is based on the equivocal tissue biopsies from the subjects with fluorescence-positive tumor. [redacted] [redacted]
Unique Aspects of this Study	This is a novel and rapidly emerging technology that may help surgeons visualize the extent of tumor or residual disease more precisely during surgery.

EXPERIMENTAL DESIGN SCHEMA

Figure 1 [redacted]

LIST OF ABBREVIATIONS

^{o}C	degrees Celsius
AE	adverse event
ALA	5-aminolevulinic acid
ALT	alanine aminotransferase
AUC	area under the curve
$AUC_{0\text{-}inf}$	AUC from zero to infinity
$AUC_{0\text{-}t}$	AUC from zero to the last measurable time point
BSA	body surface area
BUN	blood urea nitrogen
cGMP	current good manufacturing principles
CI	confidence interval(s)
CL	total body clearance
C_{max}	maximum observed concentration
CNS	central nervous system
C_0	concentration back-extrapolated to time 0
CRF	case report form
CSF	cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
CTX	Chlorotoxin
FDA	Food and Drug Administration
FI	fluorescence intensity
FIH	first in human
FN	false negative
FP	false positive
FPFV	first patient first visit
GCP	good clinical practice
GEE	general estimating equation
GFAP	glial fibrillary acidic protein
GLP	good laboratory practice(s)
GTR	gross total resection
H&E	hematoxylin and eosin
HDD	hard-disk drive

hERG	human ether-a-go-go-related gene
HIV	human immunodeficiency virus
Hr	Hour
ICG	indocyanine green
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
IND	investigational new drug application
IRB	institutional review board
ISF	investigator site file
IV	Intravenous
LC/MS	liquid chromatography / mass spectrometry
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NHP	nonhuman primate
NIR	near infrared
NOAEL	no-observed-adverse-effect-level
NPV	negative predictive value
NTR	near total resection
OS	overall survival
PEAC	Protocol Endpoint Assessment Committee
PFS	progression-free survival
PK	pharmacokinetic(s)
PPV	positive predictive value
ROI	region of interest
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SIRIS	Synchronized Infrared Imaging System
SMC	Safety Monitoring Committee
SOC	standard of care
SOP	standard operating procedure

STR	subtotal resection
T	Time
TK	Toxicokinetic
T_{max}	time of maximum observed concentration
TN	true negative
TP	true positive
$t_{1/2}$	terminal half-life
ULN	upper limit of normal
V	Volume
V_{ss}	apparent volume of distribution at steady-state
WHO	World Health Organization

1 OBJECTIVES

1.1 Primary Objectives

The primary objectives of this study in subjects undergoing neurosurgical resection of pediatric primary CNS tumors are:

- To compare the sensitivity of tozuleristide and the Canvas near infrared (NIR) imaging system fluorescence to the sensitivity of surgical designation in equivocal tissue in situ
- To compare the specificity of tozuleristide and the Canvas system fluorescence to the specificity of surgical designation in equivocal tissue in situ
- To evaluate imaging efficacy as measured by sensitivity of tozuleristide and the Canvas system in facilitating intraoperative fluorescence detection and visualization of tumor in equivocal tissue in situ
- To evaluate imaging efficacy as measured by specificity of tozuleristide and the Canvas system in facilitating intraoperative fluorescence detection and visualization of tumor in equivocal tissue in situ.

1.2 Secondary Objectives

The secondary objectives of this study are:

- [redacted]

1.3 Exploratory Objectives

The exploratory objectives of this study will evaluate the:

- [redacted]

2 BACKGROUND

2.1 Study Disease

Brain tumors are the leading cause of cancer death in children. Neurosurgical resection of gross disease remains an essential component of care and cure for the majority of pediatric brain tumors, including high-grade glioma (Yang 2013), ependymoma (Pollack 1995, Rogers 2005), medulloblastoma (Zeltzer 1999), supratentorial primitive neuroectodermal tumor (Jakacki 2015) and atypical teratoid/rhabdoid tumor (Chi 2009) as detailed in Table 1 below. Low-grade gliomas may be cured with surgery alone (Fisher 2008). Survival of patients with both low- and high-grade gliomas is enhanced with maximal tumor resection (Hervey-Jumper 2015).

Table 1 Survival in children with brain tumors according to extent of tumor resection

Tumor histology	Survival measure-ment time	Survival for children with complete resection	Survival for children with residual disease	P value	Estimated GTR rate	Reference
Glioblastoma	5-year OS	42% (n=17)	0% (n=20)	NA	~45%	Yang, 2013
Ependymoma	5-year OS	80% (n=23)	22% (n=14)	< 0.0001	~60%	Pollack, 1995
Supratentorial primitive neuroectodermal tumor	5-year OS (stage M0 tumor)	59% (n=17)	10% (n=12)	0.017	~60%	Jakacki, 2015
Medulloblastoma	5-year PFS (stage M0 tumor and ≥3 years age)	78% (n=61, includes patients with <1.5cm^2 residual tumor)	54% (n=22, includes patients with ≥1.5cm^2 residual tumor)	0.023	~75% (NTR+GTR)	Zeltzer, 1999
Atypical teratoid/rhabdoid tumor	2-year OS	91% (n=11)	NA	0.004	~55%	Chi, 2009
Low grade glioma	5-year PFS	90% (n=52)	36-48% (n=213)	<0.001	~20%	Fisher, 2008

OS: overall survival; PFS: progression-free survival; GTR: gross total resection; M0: no evidence of metastasis

Even the most experienced neurosurgeons are challenged by the difficulty of distinguishing cancer tissue from healthy brain. 5-aminolevulinic acid (ALA) is an intraoperative imaging agent that was developed and approved for clinical use in Europe for adults with glioblastoma. In a randomized controlled trial of adults with glioblastoma, ALA was significantly more likely to result in gross total resection, with 65% in the ALA group achieving gross total resection compared to 36% in the control group ($p<0.05$). In addition, the ALA group achieved a significantly ($p<0.05$) greater 6-month survival of 41% compared to 21% in the control arm (Stummer 2006). The study of ALA in adults with glioblastoma demonstrates that intraoperative imaging may have a greater impact on patient survival (20% difference) than any medical therapy developed to date, including temozolomide which resulted in 15% improvement in survival in the initial landmark study leading to United States Food and Drug Administration (FDA) approval (Stupp 2005). A recent systematic review and meta-analysis concluded that the intraoperative imaging agent ALA was superior to neuronavigation for adults with high grade glioma, resulting in improved extent of resection, survival, and quality of life (Zhao 2013). However, ALA is not likely to be applicable to pediatric use. Several reports of off-label use of ALA in children in Europe have decreased enthusiasm for developing this particular agent for pediatric use, most significant of which is the limited or lack of binding to the most common pediatric histologic types of brain tumors, low-grade lesions and embryonal tumors such as medulloblastoma (Barbagallo 2014, Beez 2014). Furthermore, ALA does not bind to brain tumor cells, but instead localizes based on blood brain barrier disruption, leading to potential false-positive and false-negative signals.

Tozuleristide (also known as BLZ-100) is a targeted fluorescent molecule designed by Blaze Bioscience to illuminate cancer foci to facilitate surgical resection. The peptide component of tozuleristide [redacted]

The fluorophore component of tozuleristide is a conjugatable form of indocyanine green (ICG). ICG is a cyanine dye that has been approved by the FDA and used as an *in vivo* fluorescent imaging agent since the 1950s. Following excitation, it has an emission wavelength higher than 800 nm which is minimally absorbed by water or hemoglobin, making it well-suited for intraoperative imaging when used with an appropriate detection device. ICG is frequently employed in vascular and ophthalmology surgery as well as for sentinel lymph node mapping. Visualization of the near infrared (NIR) fluorescence from ICG is accomplished using an imaging system, typically composed of a light source for excitation, a camera to detect NIR fluorescence and a monitor to display the images from the camera. Commercially available NIR imaging systems for ICG detection, such as the Fluobeam® 800 (Fluoptics) imaging system or the Artemis Handheld Imaging System/Spectrum (Quest Medical Imaging), [redacted]

Preclinical data show that chlorotoxin-based dye conjugates bind specifically to a range of human and animal tumors and provide greatly improved image resolution compared with pre-operative magnetic resonance imaging (MRI) or direct intraoperative observation, and greater imaging time window flexibility. Thus, they may enable surgeons to visualize and remove tumor cells that would otherwise have remained undetected and more precisely view tumor margins, resulting in more complete surgical resection.

2.2 Study Agent and Device

Agent: Tozuleristide (also known as BLZ-100) supplied by Blaze Bioscience

Investigational Agent	**IND#**	**IND Sponsor**
Tozuleristide	IND: [redacted]	Blaze Bioscience

Investigational Device	**IDE# (see note below)**	**IDE Sponsor**
Canvas NIR imaging system	IND: [redacted]	Blaze Bioscience

[redacted]

For more information on tozuleristide, please refer to the current Investigator's Brochure(s): Tozuleristide Investigator's Brochure.

For Device information, please refer to the current Canvas Imaging System Investigator's Brochure.

2.3 Nonclinical Studies

All nonclinical studies are described and summarized in the Tozuleristide Investigator's Brochure.

[redacted]

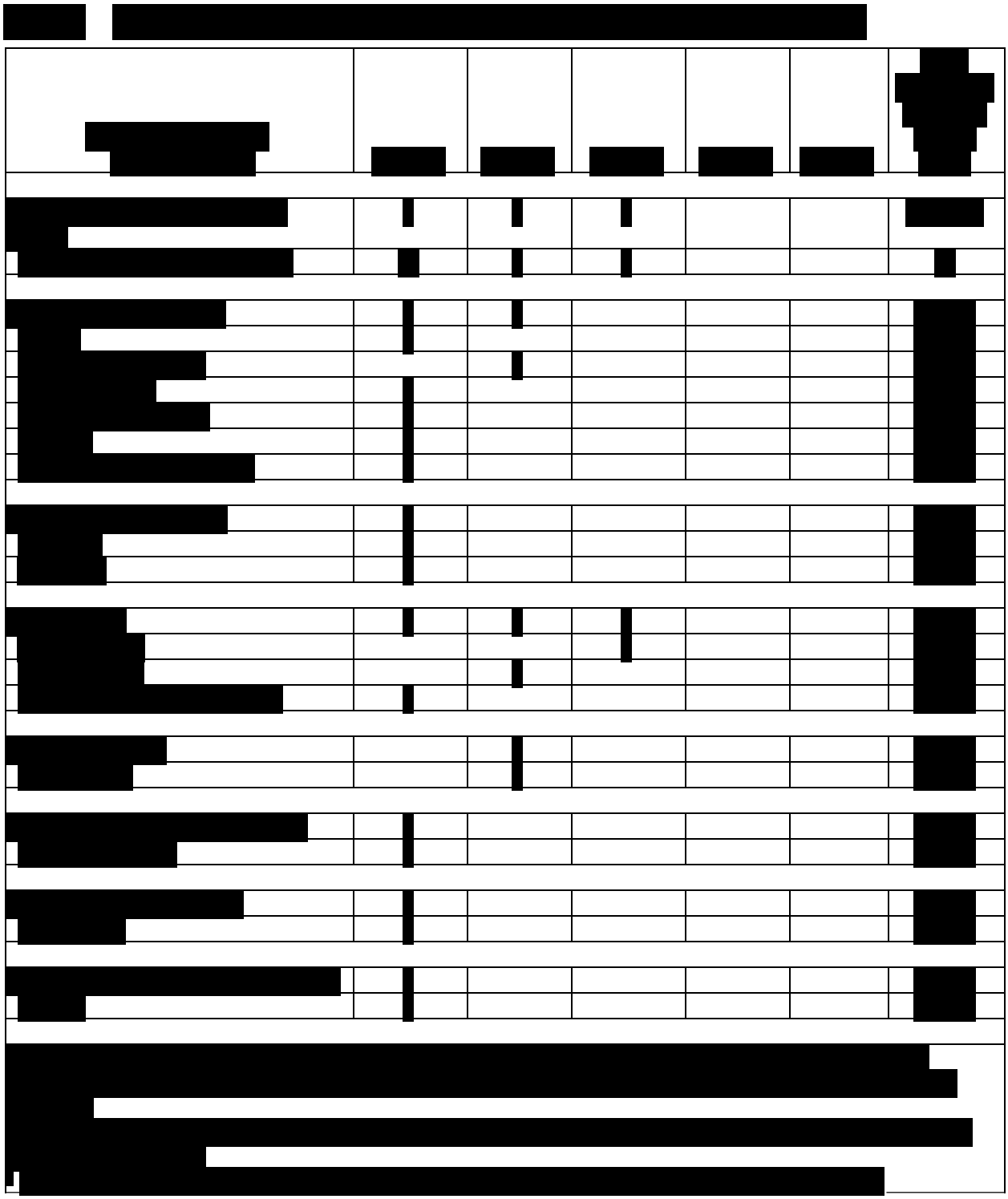
2.3.1 Safety summary: Tozuleristide

[redacted]

For the most current safety information, refer to the Tozuleristide Investigator's Brochure.

[redacted]

Overall, the clinical studies in adults and pediatrics have shown that tozuleristide appears to be safe and well-tolerated.



2.3.1.1 Serious Adverse Events

To date, there have been no tozuleristide related serious adverse events reported.

2.4 Clinical Studies

2.4.1 Overview of Clinical Studies

Table 4 provides an overview of the Phase 1 clinical studies with tozuleristide.

Table 4 Clinical studies with tozuleristide

Study No. **Phase / Status**	**Design** **Objectives**	**Population**	**Dosage of Tozuleristide and Frequency**
BB-001 Phase 1 / **Complete**	Open-label, FIH, dose-escalation/expansion study Primary objectives: safety and tolerability Secondary objectives: PK, dose level for Phase 2 studies	Adult subjects with skin cancer undergoing surgical excision of their tumor(s)	21 subjects treated 1 – 18 mg IV, single 15 minute infusion 48 hours prior to surgery
BB-002 Phase 1 / **Complete**	Open-label, dose-escalation study evaluating doses up to 30 mg Primary objectives: safety and tolerability Secondary objectives: PK, fluorescent signal from excised brain tumor tissue, dose level for Phase 2 studies	Adult subjects with glioma undergoing surgical excision of their tumor(s)	17 subjects treated 3 – 30 mg IV, single bolus administration at least two hours prior to surgery
BB-004 Phase 1 / **Complete**	Open-label, dose-escalation and expansion study Primary objectives: safety and tolerability, PK, recommended Phase 2 dose	Pediatric subjects with primary CNS tumors	[redacted]
BB-005 Phase 1 / **Complete**	Open-label, exploratory study Primary objective: safety and tolerability Secondary objectives: fluorescent signal intensity from excised tumor tissue, PK in subjects with breast cancer.	Adult subjects with solid tumors (breast, lung, prostate, colorectal, and "other") undergoing surgery	30 subjects treated [redacted] 12 mg or 6 mg IV, single bolus administration at least two hours prior to surgery

CNS = central nervous system; FIH = first in human; IV = intravenous; PK = pharmacokinetic

[redacted]

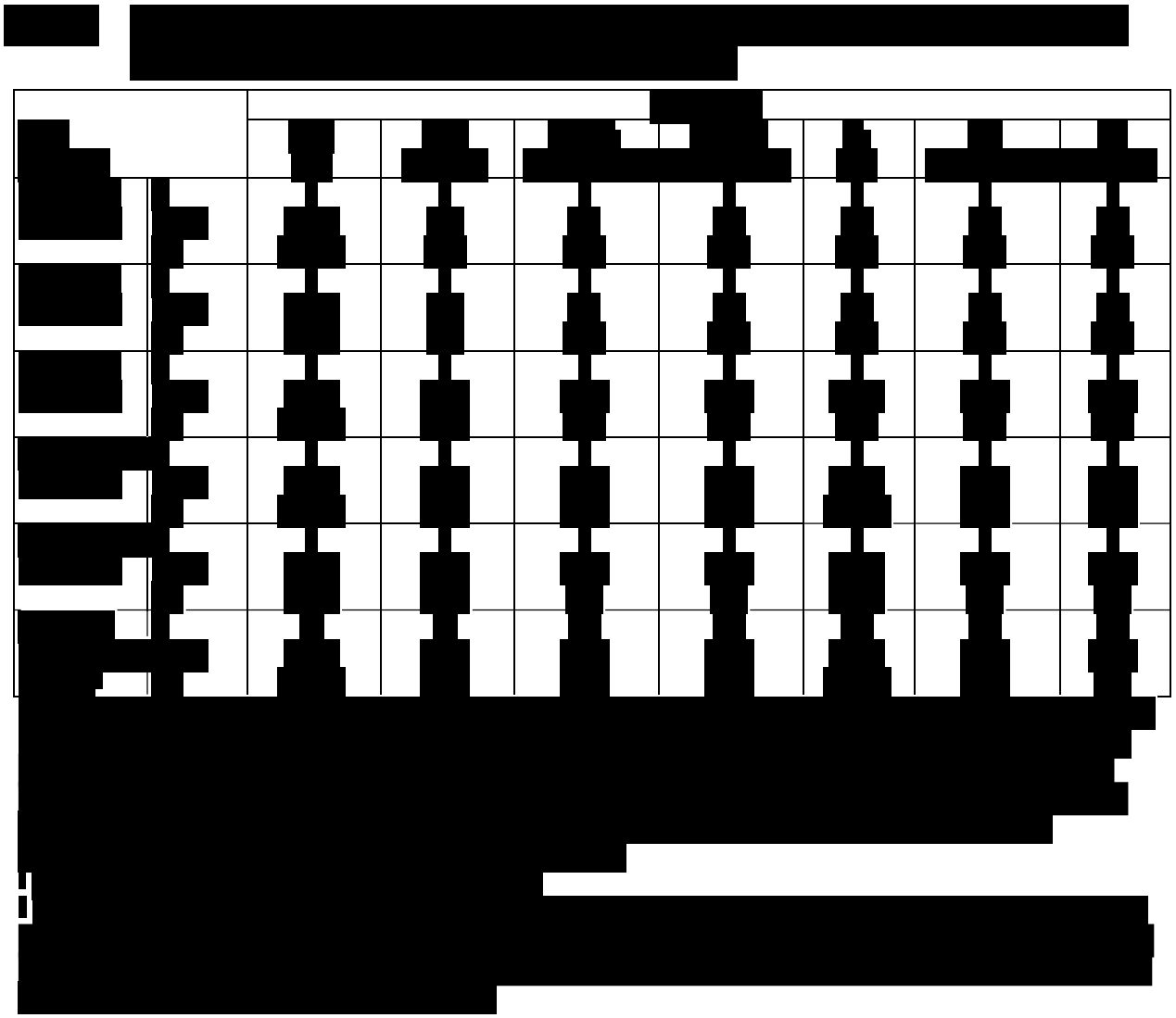
The above clinical studies are presented in detail in Tozuleristide Investigator's Brochure.

In the clinical studies to date, visualization of tozuleristide has been performed using more than one imaging system, [redacted]

[redacted]

2.4.2 [redacted]

[redacted]



[redacted]

2.4.3 [redacted]

[redacted]

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2.4.3.2 [redacted]

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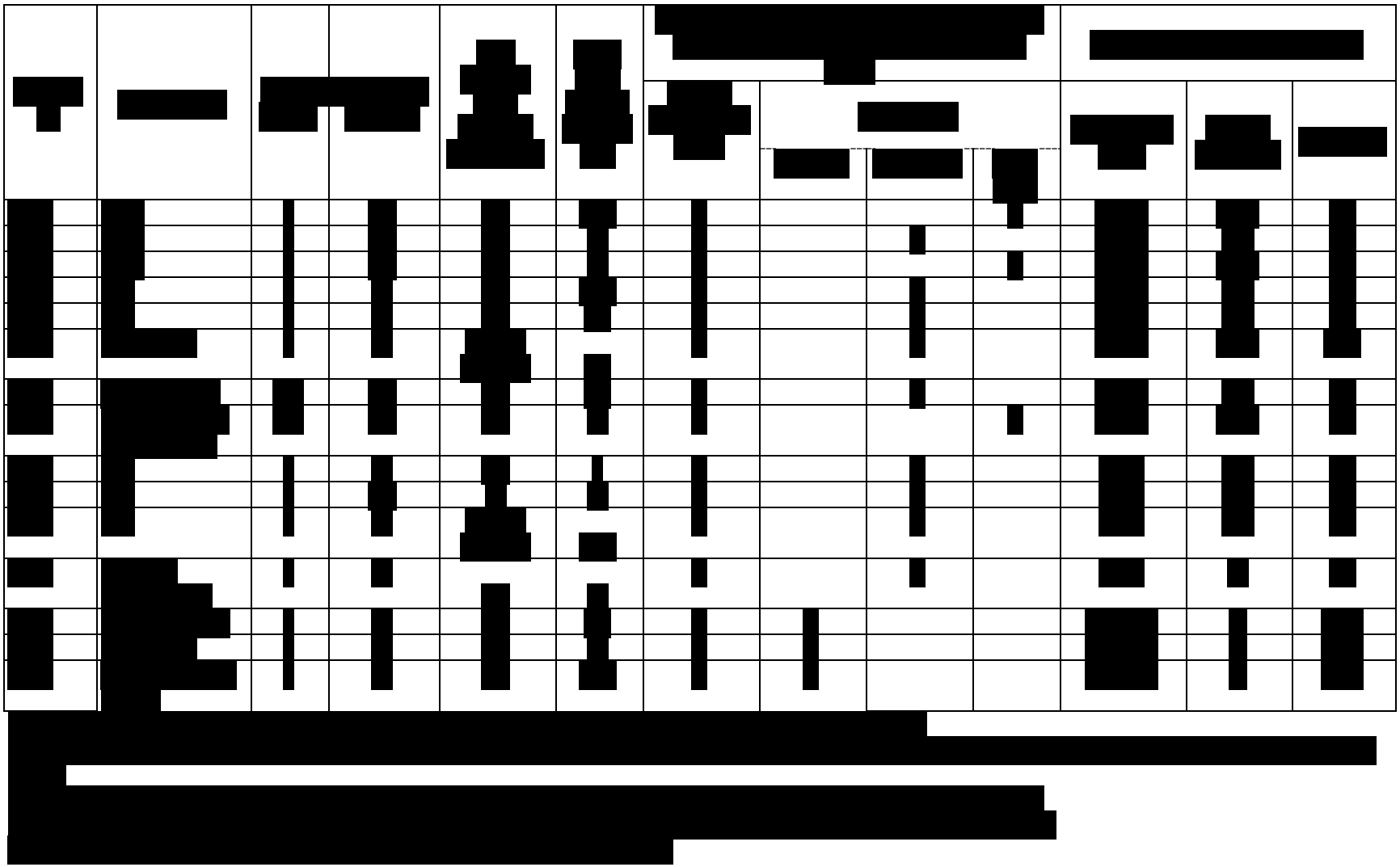

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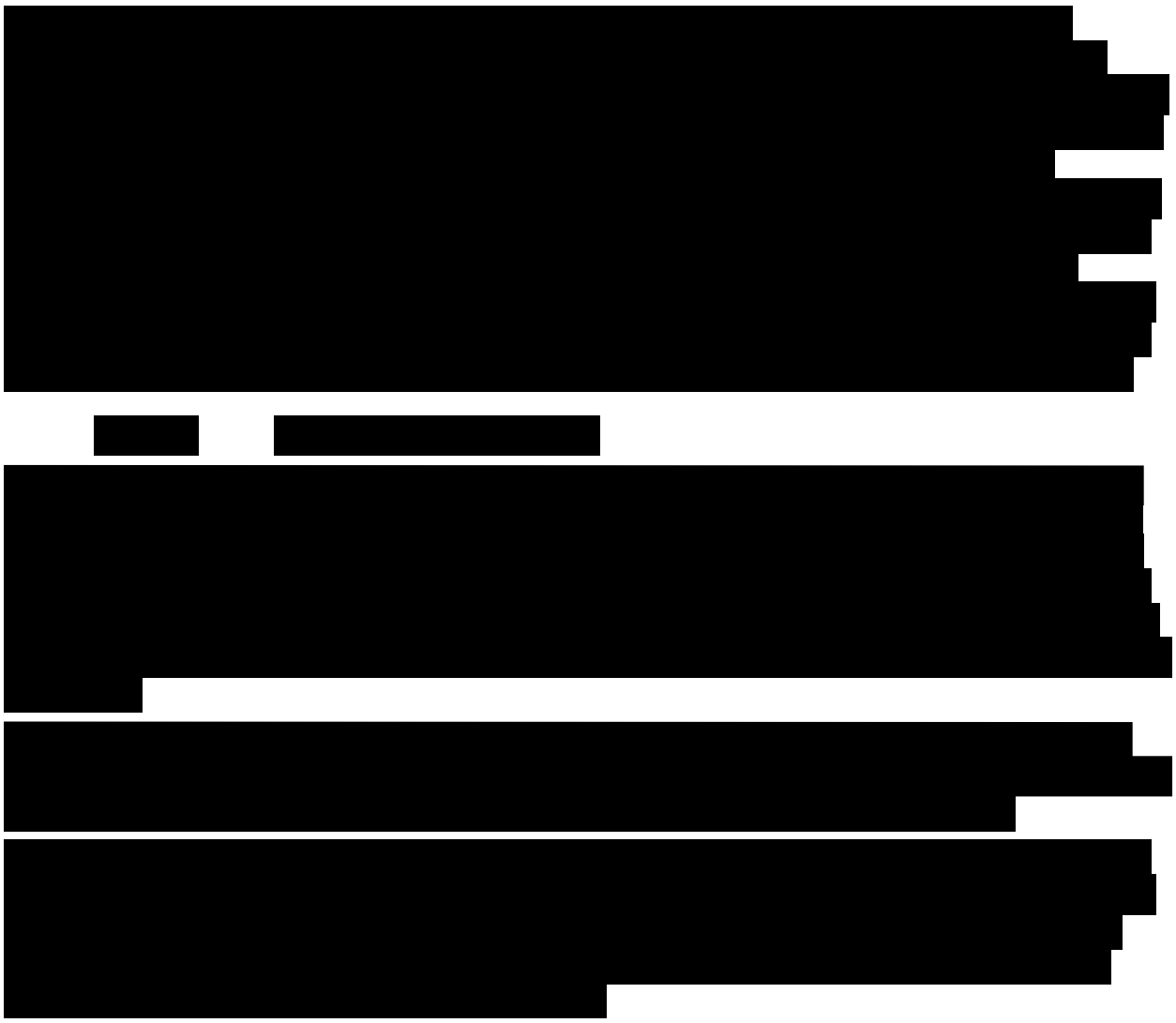

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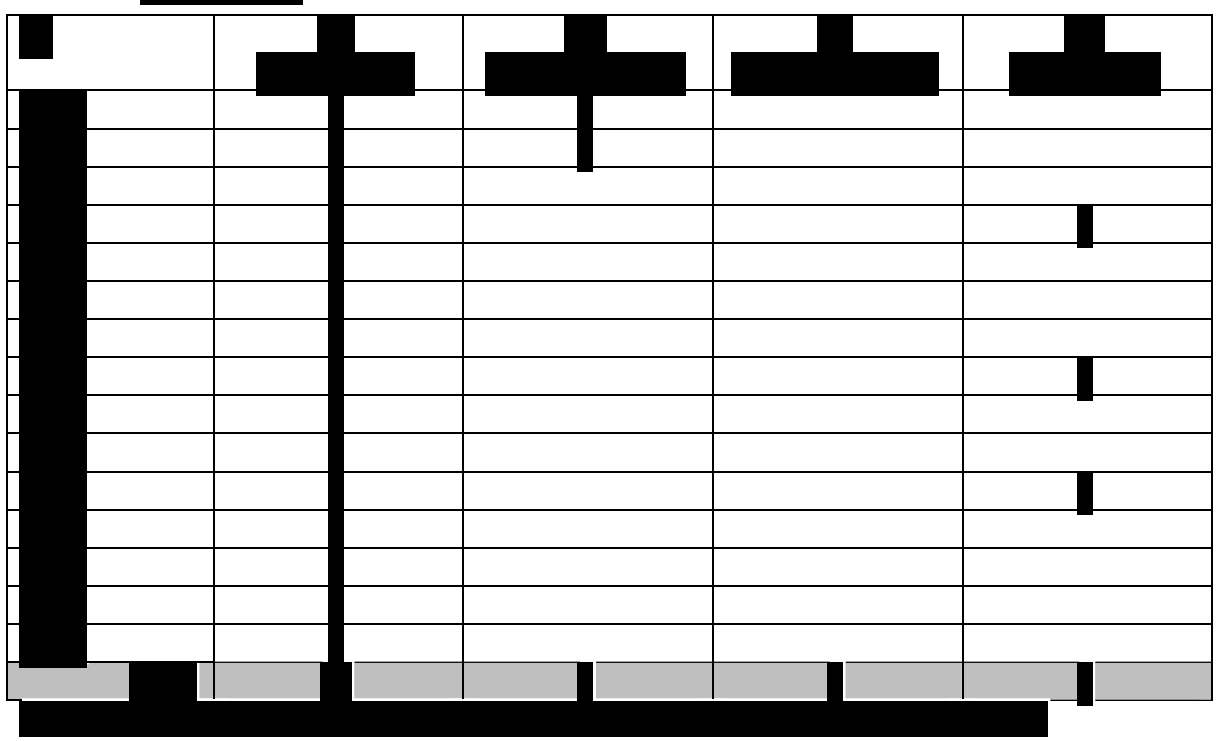

2.5 Rationale

2.5.1 Study Rationale

Brain tumors are the most common solid tumor type within the pediatric population, with about 2,500 new cases of malignant brain tumors per year (ages 0-19) in the US (Gajjar 2013). Furthermore, pediatric central nervous system cancer is the leading cause of cancer death in children (U.S. Cancer Statistics Working Group). Surgery is first-line treatment for eligible pediatric brain tumor patients (Sievert 2009, Robertson 2006). Surgical resection significantly affects chance of cure in the majority of pediatric CNS tumor types, including medulloblastoma, atypical teratoid/rhabdoid tumor, ependymoma, high-grade glioma, and low-grade glioma (Fisher 2008). However, surgical damage to healthy brain can lead to devastating long-term side effects.

Current detection techniques such as intraoperative MRI, ultrasound, positron emission tomography scanning, and magnetoencephalography are not precise enough and do not have

high surgical usefulness as these techniques are often not feasible during the time of surgery without significant disruption to the operative flow (Huang 2013).

While primary tumor may be readily recognized by an experienced neurosurgeon using visual and tactile stimuli, there are frequently areas of equivocal tissue identified during the course of a prolonged tumor resection where the goal is maximal safe surgical resection. Equivocal tissue may be present for a number of reasons including tumor invasion into normal brain, retraction artifact, gliosis, local tissue reaction to the presence of tumor, or scar tissue from previous procedures. Equivocal tissue may represent marginal or ambiguous areas where the addition of neurosurgical imaging agent such as tozuleristide may provide the most utility. For this reason, this study is designed to evaluate efficacy in these equivocal areas.

There are few other studies in pediatric neuro-oncology that have attempted to evaluate and quantitate routine neurosurgical experience with areas of equivocal tissue. In this study we will therefore focus the primary efficacy analysis on an assessment of tissue fluorescence in the operating room (local assessment) and in addition capture and compare to the routine neurosurgical assessment of equivocal tissue planned for resection.

There is an urgent unmet need for a tumor-targeted imaging agent to enable real-time intraoperative distinction between tumor and non-tumor tissue to improve neurosurgical outcomes, either as increased chance of a complete total resection or decreased risk of inadvertent normal brain resection or both.

2.5.2 Dose Rationale

Safety, pharmacokinetic, and imaging data from the Phase 1 clinical studies support a near-optimal tozuleristide dose for pediatric central nervous system tumors of ~15 mg/m^2 administered at least 1 hour before the start of surgery.

- [redacted]

2.5.3 Device Rationale

The NIR fluorescence signal from tozuleristide is not visible to the human eye. As such, an imaging device is needed to capture and display fluorescence. Additionally, while currently marketed surgical microscopes, [redacted] have features capable of detecting

ICG, they are not sensitive enough to detect fluorescence from tozuleristide.

The Canvas system, an investigational device , will be used for intraoperative imaging in this study to allow the surgeon the ability to use a fluorescence detection camera that is mounted to the optical head of the surgical microscope. No alterations in ambient light conditions are needed for the Canvas system to capture NIR images.

The Canvas system is designed to detect the NIR fluorescence of tozuleristide in the intraoperative setting of neurosurgery.

2.5.4

2.5.4.1

2.5.4.2

2.5.4.3

2.5.4.4

[redacted]

2.5.4.5 [redacted]

[redacted]

2.5.4.6 [redacted]

[redacted]

[redacted]

2.6 [redacted]

[redacted]

3 STUDY DESIGN

3.1 Characteristics

This is a randomized, blinded (central pathology, central fluorescence assessment, and central radiology), multi-center Phase 2 study of a single dose of tozuleristide in subjects with pediatric primary CNS tumors; intraoperative imaging will be performed with the Canvas system.

There will be 2 arms (randomized 1:10):

- Arm 1 (no drug treatment): ~9% of subjects
  Subject not injected with tozuleristide and undergoes standard of care neurosurgery
- Arm 2 (tozuleristide treated): ~91% of subjects
  Subject injected with tozuleristide and undergoes standard of care neurosurgery

In addition, re-treatment with tozuleristide after the initial neurosurgery may be allowed if additional neurosurgery is needed (Section 4.1.3). Data collected after re-treatment will constitute the re-treatment arm.

3.2 Number of Subjects

Approximately 114 subjects are planned.

3.3 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. Subjects must be >1 month and ≤30 years of age at the time of study enrollment
2. Subjects must have MRI obtained within 30 days of study enrollment documenting a measurable lesion consistent with a pediatric primary CNS tumor for which maximal safe resection is indicated
3. Adequate renal function defined as:
   a. Serum creatinine within normal limits for age or calculated creatinine clearance ≥75 mL/min/1.73 m^2 based on Schwartz equation or normal creatinine for age based on the following table:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

4. Adequate liver function defined as:
   a. Bilirubin <2 x upper limit of normal
   b. Alanine aminotransferase (ALT) < 3 x upper limit of normal
   c. Serum albumin >2 g/dL

5. Prior therapy: Subjects with prior therapy are eligible provided they have recovered from any acute toxic effects of prior therapy and have sufficient time interval prior to enrollment:
    a. Radiation therapy: subjects may not have had radiation therapy to the area of tumor planned to be resected within 28 days of study enrollment
    b. Chemotherapy: at least 14 days from any myelosuppressive chemotherapy (28 days if prior nitrosourea) and if prior chemotherapy, must have an absolute neutrophil count recovery of $\geq 1000/mm^3$ following count nadir
    c. Biologic: at least seven days from any anti-neoplastic biologic agent (at least three half-lives since last administration of monoclonal antibodies)
    d. Immunotherapy: at least 42 days after completion of any cellular immunotherapy, such as CAR-T cell therapy
    e. Prior surgery for CNS tumors is allowed
    f. Prior tozuleristide: at least one week after prior dose of tozuleristide if previously treated. NOTE: Subjects previously enrolled on PNOC012 study and randomized to either Arm 1 (control) or Arm 2 (treatment) will be eligible for re-enrollment for open-label treatment of tozuleristide (re-treatment) in the event another surger(ies) is clinically indicated (Section 4.1.3).

6. Written informed consent must be obtained from the subject or parent or legal guardian prior to the conduct of study activities. Routine clinical tests, e.g., MRI, clinical laboratory studies, may be used for screening requirements. Assent, when appropriate, will be obtained according to institutional guidelines.
7. The risks of treatment with tozuleristide during pregnancy have not been evaluated. Female subjects of child-bearing potential must agree not to attempt to become pregnant or undergo *in vitro* fertilization and, if participating in sexual activity that could lead to pregnancy, must use two reliable methods of contraception simultaneously for 30 days after surgery. Male subjects must agree not to attempt to father a child and, if participating in sexual activity that could lead to pregnancy, must use two reliable methods of contraception simultaneously for 30 days after surgery if their partner is of child-bearing potential. (Refer to Section 6.2.2 for reliable methods of contraception).

3.4 Exclusion Criteria

Subjects meeting any of the following criteria will be considered ineligible for this study:

1. Pregnancy and contraception: Subjects who are pregnant or breastfeeding or planning to conceive a child within 30 days are not eligible. Males and females of childbearing potential must agree to use two effective forms of contraception from the time of enrollment until 30 days post-surgery.
2. Subjects with on-going serious medical conditions (poorly controlled asthma, diabetes, heart disease) such that participation in the study could put the subject at increased risk of worsening their condition.
3. Subjects planned to undergo only a diagnostic biopsy procedure, without intent to resect tissue for therapeutic purposes (e.g., stereotactic pontine biopsy).
4. Subjects who in the opinion of the investigator are not willing or able to comply with randomization procedures or other study-required study procedures and observations.

Subjects previously enrolled and randomized to Arm 1 (control) are not eligible for re-enrollment unless a second surgery is required by standard of care.

Important note: The eligibility criteria listed above are interpreted literally and cannot be waived.

4 REGISTRATION PROCEDURES

4.1 General Guidelines

Subjects must meet all inclusion criteria and no exclusion criteria should apply. The subject must have signed and dated an approved, current version of all applicable consent forms. To allow non-English speaking subjects to participate in this study, bilingual health services will be provided in the appropriate language when feasible.

Please see Study Manual for details of enrollment procedures in the Electronic System. Enrollment checklist and source documentation must be provided for Study Chair and/or [redacted] Project Leader review and confirmation of eligibility prior to randomization.

4.1.1 Treatment Allocation

After enrollment, [redacted], subjects will be randomized 1:10 to Arm 1 (no drug treatment) or Arm 2 (tozuleristide treatment).

Arm 1: Approximately ten subjects (~9% of subjects) will not receive tozuleristide and will undergo standard of care neurosurgery.

Arm 2: Approximately 104 subjects (~91% of subjects) will receive tozuleristide at a dose of 15 mg/m^2 administered as a single IV bolus dose at least one hour and no more than 36 hours before the planned start time of surgery.

Re-treatment arm: See Section 4.1.3 below regarding re-treatment.

4.1.2 Blinding

This is a randomized, blinded (central pathology, central fluorescence assessment, and central radiology) study. A 1:10 randomization scheme will allocate ~9% of subjects to a no study drug standard of care neurosurgery arm. This will help to reduce subject selection bias and expectation of fluorescence in the operating room. [redacted]

The pathology assessment of tissue as tumor or not tumor, for both arms, will be done by a centralized and independent panel of two pathologists without knowledge of fluorescence status, surgeon's designation of tissue status or treatment arm (blinded pathology).

[redacted]

Post-operative centralized MR image assessment [redacted], for both arms, will be performed by a central and independent radiologist without knowledge of fluorescence status, treatment assignment or surgical assessment (blinded radiology).

4.1.3 Re-treatment

Subjects who are randomized to Arm 1 (no tozuleristide) or Arm 2 and need to undergo additional surgeries for their brain tumor will be eligible to receive tozuleristide without being subject to randomization. Subjects must meet all study eligibility requirements and re-consent for study prior to re-enrollment.

5 AGENT ADMINISTRATION

5.1 Investigational Product

[redacted] ozuleristide will be administered by an IV bolus injection at least one hour (and no more than 36 hours) before the subject's planned surgical tumor excision.

[redacted]

Tozuleristide will be given at an IV bolus dose of 15 mg/m^2 over approximately 1-5 minutes.

5.2 Imaging Device

[redacted].

5.2.1 Canvas System Data

For every imaging procedure, the Canvas system collects a variety of data.

[redacted]

5.3 Regimen Description

Arm 1: Approximately ten subjects.

Subjects randomized to standard of care neurosurgery arm (Arm 1) will not receive tozuleristide.

[redacted]

All clinical decision-making regarding tissue resection should be made based on the routine neurosurgical practices, and tissue resection will take place under normal light conditions in line with best clinical practices.

Arm 2: Approximately 104 subjects.

Tozuleristide will be administered as a single IV bolus dose at least one hour and no more than 36 hours before the planned start time of surgery. Tozuleristide will be given at a dose of 15 mg/m^2.

[redacted]

[redacted]

All clinical decision-making regarding tissue resection should be made based on the routine neurosurgical practices, and tissue resection will take place under normal light conditions in line with best clinical practices.

Tozuleristide and the Canvas system are intended as an aid to surgical decision-making. As such, when a region of interest is noted to be fluorescent, it is always the surgeon's decision whether to biopsy/resect if safe to do so.

5.4 *Phase 0/1* Dose Escalation Scheme

Not applicable.

5.5 *Phase 0/1* Definition of Dose-Limiting Toxicity

Not applicable.

5.6 General Concomitant Medication and Supportive Care Guidelines

Per routine preoperative and postoperative practices, subjects on study may receive steroids, anti-emetics, anti-epileptics, antibiotics or any other medications that are clinically indicated. Administration of tozuleristide is not anticipated to interfere with the standard of care for subjects on this trial.

At each study visit or contact, the investigator should question the subject or their legal representative about any medication taken, including vitamin supplements and herbal remedies. Any concurrent medications from Screening (-14 days prior to surgery) until Day 8 will be recorded in the subject's records and the case report form (CRF). Any changes in doses or introduction of new medications during this period will also be recorded. Any medications necessary for treatment of a SAE up to three months post-surgery should be recorded in the subject's CRF.

5.6.1 Special Dietary Requirements

There are no special dietary requirements.

5.6.2 Concurrent Medications / Treatments Not Permitted

5.6.2.1 Prior to Study Entry

None

5.6.2.2 On Study

- ***Concurrent Anticancer Therapy***
  Subjects may begin other appropriate anti-cancer therapy including chemotherapy and/or radiation therapy, but they will be considered off study for safety endpoints on the day when further tumor-directed therapy is initiated.
- ***Supportive Care***
  No specific supportive care is recommended related to tozuleristide. Subjects should continue to receive all routine preoperative and postoperative supportive care, including

steroids, blood products, fluids, and prophylaxis or treatment of pain, nausea, vomiting, seizures, or infection. Allergic reaction may occur with any medication and should be managed per institutional guidelines.

- ***Pregnancy***
  If a subject on study is found to be pregnant or the partner of a male subject becomes pregnant within 30 days of study drug administration, then the possible prenatal exposure to study drug should be promptly reported.

5.7 Dosing Modifications and Delays

No dosing modifications are expected.

5.7.1 Criteria for dose-modification in case of suspected tozuleristide toxicity and re-initiation of treatment

Since tozuleristide is given as a single IV bolus; no dose modifications are expected.

6 TREATMENT PLAN

6.1 Study Calendar

[redacted].

[redacted]

6.2 Observations and Procedures

6.2.1 Informed Consent

- Signed informed consent: Protocol and consent documents must be approved by the IRB prior to subject enrollment. The investigational nature and objectives of the trial, procedures involved, potential risks and discomforts, and alternative options will be carefully explained to the subject and/or the subject's parents or guardian, and a signed informed consent and assent, if appropriate, will be obtained according to institutional guidelines. Informed consent must be obtained prior to obtaining any study specific observations that are outside of standard clinical care in order to determine study eligibility.

6.2.2 Screening Period (Day -14 to day of surgery)

- Eligibility criteria: Before the subject is enrolled, a site investigator must sign and date a completed eligibility checklist verifying review and determination that the subject meets all eligibility requirements and does not meet any exclusion criteria. These criteria and supporting information will be reviewed by the study chair or back-up and confirmed by the [redacted] lead or back-up prior to randomization.

  Eligibility criteria (inclusion and exclusion criteria) cannot be waived. Clinical and laboratory data to determine eligibility must be available in the subject's medical or research record which will serve as source documentation for verification at the time of audit.

  In order to assess any potential impact on subject eligibility with regard to safety, the investigator must refer to the relevant document(s) for detailed information regarding warnings, precautions, contraindications, AEs, and other significant data pertaining to the

tozuleristide study drug product and the Canvas system being used in this study. Such documents may include, but are not limited to, the Investigator's Brochure or equivalent document(s) provided by Blaze Bioscience.

Subjects will be eligible for enrollment once all screening tests and procedures are completed and results indicate that all eligibility criteria have been met. Once approved, subjects will be randomized 1:10 to Arm 1 (no drug treatment, standard of care neurosurgery) or Arm 2 (tozuleristide treatment). Subjects on re-treatment arm will be assigned a new subject number and not be subject to randomization, but still must go through the study eligibility and approval process.

- Demographics
- Medical history
- Medication history
- Body weight
- Height
- Performance status: See Appendix A
- Physical examination
- Concurrent medications
- Measurement of clinical chemistry parameters: Sodium, Potassium, Chloride, CO2, blood urea nitrogen (BUN), creatinine, alanine aminotransferase (ALT), bilirubin, albumin.
- Measurement of hematology parameters: Complete blood count (red blood cells, white blood cells with differential, platelets), hemoglobin and hematocrit.
- Measurement of coagulation parameters: PT/INR and PTT.
- Pregnancy test (for females of childbearing potential): All women of child bearing potential (defined as sexually mature female who has had menses within the preceding 24 months and has not undergone hysterectomy, bilateral oophorectomy, or tubal ligation) must have a negative pregnancy test (urine or serum test with a sensitivity of at least 50 IU/mL) performed at Screening/ Baseline.

  Women of childbearing potential must agree not to attempt to become pregnant or undergo *in vitro* fertilization and, if participating in sexual activity that could lead to pregnancy, must use two reliable methods of contraception simultaneously for 30 days after surgery. Male subjects must agree to use two reliable methods of contraception simultaneously for 30 days after surgery if their partner is of child-bearing potential.

  A combination of two of the following methods must be used:

  - Condoms (male or female) with spermicide
  - Diaphragm or cervical cap
  - Intrauterine Device
  - Hormonal-based contraception
  - Vasectomy

  Women (including pre-pubescent females) who are not of reproductive potential are not

required to use contraception.

- MRI of tumor: MRI with and without contrast prior to treatment should be obtained within 30 days of enrollment. MRI sequences should include T1 pre-contrast, T1 post-contrast, T2, FLAIR, and Diffusion weighted images. [redacted] For recommended imaging protocol and sequence parameters, please see Appendix F. [redacted] All MRI processes for central radiology will be detailed in the study reference manual.
- [redacted]

6.2.3 1 to 36 Hours Pre-Surgery

- ECG (Arm 2 and re-treatment arm only): On the day of tozuleristide dosing, a baseline ECG will be obtained prior to dosing (within 24 hours), and an additional ECG will be obtained 1-30 minutes post-end of dose. ECG recordings will be performed once the subject should have been resting semi-supine for at least ten minutes and will be measured in triplicate over approximately 3 minutes (with wait time of approximately one minute between recordings). A 12-lead ECG recording will be performed in a standardized manner as outlined in the Study Reference Manual. Repeat measurements will be performed if any clinical abnormalities are observed or if artifacts are present.
- Vital signs obtained pre-surgery (Arm 1) or pre-dose and 1-30 minutes post-end of dose (Arm 2 and re-treatment arm).
- Concurrent medications: continuous assessment
- Adverse events: continuous assessment
- Study drug administration (Arm 2 and re-treatment arm only): Tozuleristide is to be administered at least 1 hour (and no more than 36 hours) before the planned start of the surgical excision of the tumor.
- [redacted]

6.2.4 Day 1 (Day of Surgery)

- Imaging and pathology during surgery (for all subjects)
- [redacted]
    - Surgery will be conducted according to standard of care procedures, including for tumor approach and resection [redacted] All clinical decision making should be made based on routine neurosurgical practices and tissue resection will

take place under normal light conditions in line with best clinical practice

- [redacted]
- [redacted]

[redacted]

1. [redacted]

- [redacted]

[redacted]

1. [redacted]

7. [redacted]

[redacted]

[redacted]

[redacted]

- [redacted]

- Concurrent medications: continuous assessment
- Adverse events: continuous assessment

- MRI of tumor: MRI with and without contrast should be obtained within 72 hours of surgery including the site of primary tumor. MRI sequences should include T1 pre-contrast, T1 post-contrast, T2, FLAIR, and Diffusion weighted images. For recommended imaging protocol and sequence parameters, please see Appendix F. Images will be evaluated by site radiology for patient management and local assessment [redacted]. Images will be made available for central imaging review [redacted] All MRI processes for central radiology will be detailed in the study reference manual.
- [redacted]

6.2.5 Day 8 (7 Days Post-Surgery ± 3 days)

- Performance status
- Physical examination
- ECG (Arm 2 and re-treatment arm only): An ECG will be obtained at seven days post-surgery. ECG recordings will be performed once the subject has been resting semi-supine for at least ten minutes and will be measured in triplicate over approximately three minutes (with wait time of approximately 1 minute between recordings). A 12-lead ECG recording will be performed in a standardized manner as outlined in the Study Reference Manual. Repeat measurements will be performed if any clinical abnormalities are observed or if artifacts are present.
- Vital signs
- Concurrent medications: continuous assessment
- Adverse events: continuous assessment
- Measurement of clinical chemistry parameters (Arm 2 and re-treatment arm only)
- Measurement of hematology parameters (Arm 2 and re-treatment arm only)
- [redacted]

6.2.6 30 Days Post-Surgery (±7 days)

- Adverse events
    - Chart review and/or telephone contact if no patient visit is documented to collect survival, [redacted], brain and spine MRIs, toxicity assessment and disease status information.
- Urine or serum pregnancy test (for females of childbearing potential)

6.2.7 2 Months Post-Surgery (±7 days) and 3 Months Post-Surgery (±7 days)

- Adverse events
    - Monthly chart review and/or telephone contact if no patient visit is documented to collect survival, [redacted], brain and spine MRIs, toxicity assessment and disease status information. Any subject receiving additional therapy for their CNS tumor, including chemotherapy and/or radiation therapy within 3 months of surgery will be considered off study for safety

observations at the time of starting additional therapy. Safety data in these subjects will be included up to the time the subject begins additional tumor-directed therapy.

- [redacted]

6.3 Off-Treatment Criteria

A subject may be removed from protocol therapy after enrollment but prior to receiving study drug for any of the following reasons:

- Withdrawal of consent for treatment
- Subject is unable to receive study drug for any reason
- Pregnancy

The study may be terminated at any point in time at the discretion of the sponsor (See Section 11.3.6).

6.4 Off Study Criteria

Subjects will be considered Off Study for the following reasons:

- Physician determines that study participation is not in subject's best interest.
- Study is terminated by the Sponsor.
- Parent, subject, or guardian withdraws consent or assent for continued participation.
- Subject death.
- Completion of protocol specific follow up period, three months following surgery
- Any subject receiving additional therapy for their CNS tumor, including chemotherapy and/or radiation therapy within three months of surgery will be considered off study for safety observations at the time of starting additional therapy. Safety data in these subjects will be included up to the time the subject begins additional tumor-directed therapy. Any on-going adverse events (AEs) at the time of off-study will be considered unresolved.

The date and reason for the subject coming off study must be documented in the case report form. Subjects coming off study due to start of additional therapy are considered to have completed study as planned.

[redacted]

7 ADVERSE EVENTS

An AE or adverse experience is any untoward medical occurrence in a subject who is administered an investigational product (whether it is the experimental product or the control) and which does not necessarily have a causal relationship with the investigational product. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Pre-existing events that increase in frequency or severity or change in nature during or as a consequence of use of a drug in human clinical trials, will also be considered as AEs. AEs may also include pre- or post-treatment complications that occur as a result of protocol-mandated procedures (e.g., invasive procedures such as biopsies).

For investigational medical devices, adverse events are any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the investigational medical device. An adverse device effect is an adverse event related to the use of the investigational medical device. It can include adverse events from insufficient or inadequate instructions for use, deployment, implantation, installation or operation, or any malfunction of the investigational device.

Any medical condition or laboratory abnormality with an onset date before randomization is considered pre-existing and should be recorded on the medical history CRF page(s).

AEs will be collected from time of randomization through three months after surgery or until start of other tumor-directed therapy, whichever is earlier. After the Day 8 visit, all subjects will be followed by chart review and/or telephone contact if no patient visit is documented every month for three months, or until start of other tumor-directed therapy (chemotherapy, radiation therapy or other investigational therapy), whichever is sooner.

If the patient experiences an AE considered to be related to study products, then the patient will be followed until resolution of that AE or until they are off study (whichever is earlier).
An AE does not include:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion); the condition that leads to the procedure is an AE
- Pre-existing diseases or conditions present or detected prior to randomization that do not worsen
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions)
- Overdose of either study product or concomitant medication without any signs or symptoms unless the subject is hospitalized for observation

7.1 Adverse Event Characteristics

All AEs will be assessed by an investigator and recorded in the subject medical record, including the time and date of onset and resolution (where possible), severity, relationship to study product (tozuleristide, Canvas system, or both), relationship to neurosurgery, and outcome.

Severity should be recorded and graded according to the CTCAE Version 5.0. In the absence of a specific toxicity grade, the following grading should be used:

Table 9 CTCAE Grading Scale

Grade	Severity	Comments
1	Mild	Aware of sign or symptom, but easily tolerated
2	Moderate	Discomfort enough to cause interference with usual activities
3	Severe	Incapacitating with inability to work or perform usual activities
4	Life-threatening	Participant is at immediate risk of death
5	Fatal	Death

The relationship to study product (tozuleristide, Canvas system, or both) and to neurosurgery should be assessed using the following definitions:

1. Related: There is a reasonable causal relationship between study drug administration/device/procedure and the AE
2. Not related: There is not a reasonable causal relationship between study drug administration/device/procedure and the AE

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship

All AEs, regardless of severity, causality, or seriousness, will be reported from the date of randomization until three months after surgery or until start of tumor-directed therapy, whichever is earlier. After the Day 8 visit, all subjects will be followed by chart review and/or telephone contact if no patient visit is documented every month for three months, or until an off-study criterion is met, to collect survival, CSF cytology if clinically indicated, brain and spine MRIs, toxicity assessment and disease status information.

7.1.1 Serious Adverse Events

A SAE is defined as follows:

Any adverse drug or medical device experience that results in any of the following outcomes:

- Death
- Life-threatening situation (subject is at immediate risk of death)
- Inpatient hospitalization or prolongation of existing hospitalization for an adverse event (excluding those for study therapy or placement of an indwelling catheter, unless associated with other serious events)
- Persistent or significant disability/incapacity
- Permanent impairment or a body structure or a body function
- Congenital anomaly/birth defect in the offspring of a subject who received study product or led to fetal distress or fetal death
- Other: Important medical events that may not result in death, be immediately life-threatening, or require hospitalization, may be considered a SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are:
    - Intensive treatment in an emergency room or at home for allergic bronchospasm

- Resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function
- Development of drug dependency or drug abuse

7.1.1.1 Clarification of Serious Adverse Events

Death is an outcome of an AE and not an AE in itself.

All deaths of subjects on study, regardless of cause, must be reported to Blaze Bioscience.

"Life-threatening" means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death, if it had occurred with greater severity.

Complications that occur during hospitalizations are AEs. If a complication prolongs hospitalization, it is a SAE.

The investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. When available, a diagnosis should be documented as the AE and/or SAE and not the individual signs/symptoms.

"In-patient hospitalization" means the subject has been formally admitted to a hospital for medical reasons, for any length of time.

The following hospitalizations are not considered SAEs:

- A visit to the emergency room or other hospital department <24 hours, that does not result in admission (unless considered an important medical or life-threatening event).
- Hospital admission for observation only does not constitute an SAE
- Elective surgery, planned prior to signing consent
- Admissions as per protocol for a planned medical/surgical procedure
- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)
- Extended hospitalization due to recovery from surgery associated with study

7.1.2 Life-threatening

An adverse event or suspected adverse reaction is considered *life threatening* if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

7.2 Adverse Event Reporting

The study period during which AEs must be reported begins after randomization and ends three months following surgery or until start of other tumor-directed therapy, whichever is earlier. For subjects on the re-treatment arm, AE reporting begins once the subject is confirmed eligible and is thus enrolled on the re-treatment arm.

After the Day 8 visit, all subjects will be followed by chart review and/or telephone contact every month for three months, or until an off-study criterion is met, to collect survival, CSF cytology if clinically indicated, brain and spine MRIs, toxicity assessment and disease status information.

If the patient experiences an AE considered to be **related** to study products, then the patient will be followed until resolution of that AE or until the patient is off study (whichever is earlier).

The Investigator will assign attribution of the possible association of the event with tozuleristide or the Canvas system or both, or to neurosurgery, and this information will be entered into the appropriate case report form. The Investigator must also comply with all reporting requirements to their institutional Data and Safety Monitoring Committee and Institutional Review Board (IRB).

7.3 SAEs and Expedited Reporting

Blaze Bioscience has requirements for the expedited reporting of SAEs that meet specific criteria of the appropriate regulatory authorities; therefore, all appropriate parties must be notified as soon as possible and within 24 hours of the investigator becoming aware of the event. The procedures for reporting all SAEs, regardless of causal relationship, are as follows:

- In the case of a SAE, information should be recorded on a SAE Report Form and faxed or emailed to the contacts below.
- Initial SAE notification can be done by email but must be with 24 hours

[redacted]

For fatal or life-threatening events, also send copies of hospital case reports, autopsy reports, and other documents when requested and applicable.

Blaze Bioscience may request additional information from the investigator to ensure the timely completion of accurate safety reports.

The investigator must take all therapeutic measures necessary for resolution of the SAE. Any medications necessary for treatment of the SAE must be recorded in the concomitant medication section of the subject's CRF.

An SAE may qualify for reporting to regulatory authorities if the SAE is considered to have a possible causal relationship to the study product and is unexpected/unlisted based upon the current Investigator's Brochure. In this case, all investigators will receive a formal notification describing the SAE.

Where this is required by local regulatory authorities, and in accordance with the local institutional policy, the investigator should notify (in writing) the IRB of SAEs according to local guidelines.

7.4 Toxicity Management

7.4.1 Definitions

The grading of AEs and abnormal laboratory values will be based on the guidelines provided in the CTCAE Version 5.0.

For the purpose of monitoring toxicities, the baseline value is defined as the last value prior to randomization. This value must be obtained from the laboratory appointed to analyze study samples. All management is based on changes from this value.

7.4.2 Guidance for Dose Modification or Discontinuation of Treatment

Dosing will be stopped if suspected adverse drug reactions, changes in vital signs, or clinical laboratory results are observed, and these changes pose a significant health risk.

If the patient experiences an AE considered to be related to study products, then the patient will be followed until resolution of that AE or until they are off study (whichever is earlier).

7.4.3 Warnings and Precautions

There are no specific warnings or precautions for tozuleristide.

For further information regarding warnings and precautions with the study product, please refer to the current Tozuleristide Investigator's Brochure.

8 [redacted] SPECIAL STUDIES

8.1 [redacted]

[redacted]

8.2 Investigational Device Information

Refer to Section 5.2 for information of the Canvas system. Detailed information is also provided in the current Canvas Imaging System Investigator's Brochure.

8.3 [redacted]

[redacted]

9 EVALUATION CRITERIA

9.1 Independent Safety Monitoring Committee (SMC)

The SMC's responsibilities are to:

- Review the protocol and plans for data safety and monitoring;
- Conduct regular interim and final evaluation of study safety including aggregate and individual subject data related to safety, data integrity, and overall conduct of the study;
- Consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on participant safety, scientific integrity, or the ethics of conducting the study;
- Protect the safety of the study subjects;
- Review and evaluate ad hoc safety issues concerning the study at the request of Blaze Bioscience;
- Make recommendations to Blaze Bioscience concerning continuation, termination, or other modifications of the study based on the observed beneficial or adverse effects of the study; and
- Operate according to the procedures described in the [redacted] charter and all procedures of the SMC.

9.2 Central Radiology

- [redacted]
- [redacted]
- [redacted]
- All MRI processes for central radiology are detailed in the study reference manual.

9.3 Central Pathology

- Primary tumor tissue specimens and equivocal tissue specimens will be required for central pathology assessment of presence or absence of tumor. Central pathology samples will be requested after completion of site final pathology report for standard clinical management. "Other biopsy" tissue specimens, if obtained, will also be evaluated by central pathology.
- [redacted]

- [redacted]
- Central pathology will be blinded to treatment allocation and fluorescence data but will have access to routine pathology data (gross and microscopic pathology reports), images and/or slides for microscopic evaluation, and molecular/genetic data.
- [redacted]

9.4 [redacted]

[redacted]

9.5 Protocol Endpoint Assessment Committee (PEAC)

The PEAC will monitor the progress of the study [redacted] Enrollment will be halted once sufficient data (specimens and sub-groups) are available for analysis.

[redacted]

Roles and responsibilities are outlined in the PEAC study charter.

10 STATISTICAL CONSIDERATIONS

10.1 Study Design/Endpoints

The study design is presented in Section 3.

[redacted]

10.1.1 Primary Endpoints

The primary efficacy endpoints are:

1. Ratio of sensitivity of tozuleristide fluorescence in equivocal tissue biopsies from subjects with fluorescence-positive tumors compared to the sensitivity of surgical designation from the same biopsies under white light conditions
2. Ratio of specificity of tozuleristide fluorescence in equivocal tissue biopsies from subjects with fluorescence-positive tumors compared to the specificity of surgical designation from the same biopsies under white light conditions
3. Sensitivity of tozuleristide fluorescence to detect tumor in equivocal tissue biopsies from subjects with fluorescence-positive tumor
4. Specificity of tozuleristide fluorescence to detect tumor in equivocal tissue biopsies from subjects with fluorescence-positive tumor

[redacted]

10.1.2 Secondary Endpoints

The secondary efficacy endpoints are:

1. [redacted]
2. [redacted]

Study endpoints related to the safety objective:

1. All reported adverse events (AEs) will be graded according to the National Cancer Institute's Common Terminology for Adverse Events (NCI CTCAE, Version 5.0)
2. SAEs
3. AE attribution of relatedness to tozuleristide and/or Canvas system (related vs. unrelated).
4. Laboratory parameters
5. ECG parameters
6. Vital signs

[redacted]

[redacted]

10.1.3 Exploratory Endpoints

[redacted]

10.2 Statistical Analysis Plan

In general, descriptive statistics will be provided for all study endpoints. Descriptive statistics will include number of subjects, mean, standard deviation, median, and range (minimum, maximum) for continuous variables, and frequencies and percentages for categorical variables. Statistical tests will be performed at either a one-sided significance level of 2.5% or a two-sided

significance level of 5%. All confidence intervals (CIs) will be constructed at a two-sided 95% confidence level.

In addition, data collected after re-treatment will be listed and will not be included in the efficacy and safety analyses.

10.2.1 [redacted]

[redacted]

10.2.2 Analysis Populations

The full analysis population (FAP) for efficacy analyses will consist of all subjects who

1. meet all eligibility criteria
2. undergo neurosurgery and

3. have central pathology tumor assessment and imaging operator fluorescence assessment of equivocal tissue specimens obtained from the first neurosurgery on study.

Study subjects in the full analysis population will be classified into four treatment groups:

- **Group 1** (Arm 1): subjects who do not receive tozuleristide, regardless of fluorescence outcomes and tumor diagnosis
- **Group 2** (Arm 2 Fluorescent): subjects who receive tozuleristide, have at least one fluorescence-positive study tissue specimens of any type (primary, equivocal and other) based on imaging operator fluorescence assessment, and the subject's central pathology consensus diagnosis is tumor, ambiguous, or not definitive
- [redacted]

A subject is evaluable for efficacy if the subject meets the three criteria of the FAP [redacted]

The safety analysis population will consist of all subjects who receive any amount of tozuleristide or receive neurosurgery prior to any re-treatment. Safety data collected in the re-treatment portion of the study will be listed separately.

[redacted]

10.2.3 Subject Disposition

An accounting of subject disposition will be tabulated by treatment arm. The number of subjects in each analysis population will be summarized by treatment arm. Subjects who withdraw from the study prematurely will be summarized. The reason(s) for study discontinuation will be summarized. The number of subjects who do not undergo surgery will also be summarized by treatment arm.

10.2.4 Demographics and Subject Characteristics

Demographic and other baseline characteristics will be summarized with descriptive statistics by treatment arm.

10.2.5 Analyses of Primary Efficacy Endpoints

The primary efficacy analyses will be based on Group 2 in the full analysis population (Section 10.2.2). The four sets of statistical hypotheses will be evaluated by assessing the statistical significance of the co-primary endpoints.

[redacted]

10.2.6 [redacted]

[redacted]

10.2.7 Study Product Exposure

The dose of tozuleristide administrated in volume (mL) and amount (mg) will be summarized [redacted]

10.2.8 Safety Analyses

All safety summaries will be tabulated for subjects who receive tozuleristide and subjects who do not receive tozuleristide in the safety population. Safety data collected in the re-treatment portion of the study will be listed separately.

10.2.8.1 Adverse Events

Adverse events will be coded using MedDRA 21.0. Adverse events will be defined as treatment-emergent if they are newly occurring or worsen following surgery (Arm 1) or treatment with tozuleristide (Arm 2 and re-treatment). Adverse events will be scored for severity using NCI CTCAE version 5.0 if applicable, or the protocol specified severity stated in Section 7.1.

All adverse events (AEs) and SAEs collected during the study will be graded according to the National Cancer Institute's Common Terminology for Adverse Events (NCI CTCAE, Version 5.0) along with attribution of relatedness to tozuleristide and/or Canvas system and neurosurgery (related vs. unrelated).

Treatment-emergent AEs, SAEs, severity of AEs, tozuleristide-related AEs, Canvas-related AEs, neurosurgical-related AEs, and AEs leading to withdrawal from study will be summarized by MedDRA preferred term and system organ class. In the event of multiple occurrences of the same AE with the same preferred term in the same subject, the AE will be counted once at the greatest severity/relatedness.

10.2.8.2 Clinical Laboratory Parameters, ECG and Vital Signs

Laboratory parameters will be summarized with descriptive statistics of the change from baseline value by time point. For laboratory parameters defined in CTCAE, shifts of baseline grade to the worse post-baseline grade will also be presented. Subject laboratory values will be listed with toxicity grades and out-of-range flags.

ECG parameters, including QT and QTcF will be summarized with descriptive statistics per time point. Changes from baseline for individual QT/QTcF will be reported as both absolute values (e.g., >450 ms) and relative changes (e.g., > 30 ms). If available, out of range ECG parameters will be assessed for the presence of genetic factors that could contribute to the abnormal ECG findings. ECG data will also be analyzed as a function of pharmacokinetic exposure measures.

10.2.9 [redacted]

[redacted]

10.2.10 [redacted]

[redacted]

10.2.11 [redacted]

[redacted]

10.2.12 Interim Analysis

Interim analysis is not planned. [redacted]

10.3 Sample Size

Approximately 114 subjects are planned for treatment in this study.

[redacted]

[redacted]

10.4 Stratification Factors

The randomization procedure will not be stratified. Permuted block randomization will be used.

11 DATA REPORTING / REGULATORY REQUIREMENTS

11.1 Data Reporting

11.1.1 Method

The investigator will ensure that this study is conducted in full conformance with the protocol, the "Declaration of Helsinki" prior to 2000 and its amendments, and with the requirements of national drug and data protection laws of the countries in which the research is conducted.

11.2 Record Keeping and Record Retention

It is the responsibility of the investigator to obtain written informed consent from each subject participating in this study or legally acceptable representative prior to undertaking any study related procedures. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study. Assent, when appropriate, will be obtained according to institutional guidelines.

The investigator must utilize an IRB-approved consent form for documenting written informed consent. The original signed and dated informed consent form must be retained in accordance with institutional policy, and a copy of the signed consent form must be provided to the subject or legally acceptable representative.

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified.

These documents should be classified into two separate categories:

- Investigator's Site File (ISF), and
- Subject clinical source documents

The ISF will contain the protocol/amendments, CRFs, query forms, IRB approval with correspondence, informed consent, drug records, staff curriculum vitae, and authorization forms, and other appropriate documents and correspondence.

Subject clinical source documents include subject hospital/clinic records, physician's and nurse's notes, appointment books, original laboratory reports, ECG, electroencephalogram, X-ray, MRI, pathology and special assessment reports, and consultant letters. All clinical study documents, including documents created or modified in electronic format, must be retained by the Investigator for at least 15 years following the completion of the study or until at least two years after the last approval of a marketing application in an ICH region (USA, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or if no application is filed or if the application is not approved for such indication, until two years after the investigation is discontinued and regulatory authorities have been notified. The investigator must notify Blaze Bioscience, prior to destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Blaze Bioscience must be notified in advance.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Blaze Bioscience to store these in a sealed container(s) offsite so that they can be returned to the

investigator in case of a regulatory audit. Where source documents are required for the continued care of the subject, appropriate copies should be made for storage offsite.

When requested in writing by the Sponsor, unused study medication supplies may be returned to the Sponsor or destroyed by the investigator. Records shall be maintained by the investigator of any such disposition of the study medication. These records must show the identification and quantity of each unit disposed of, the method of destruction (taking into account the requirements of local law), and the person who disposed of the test substance. Such records shall be submitted to the Sponsor.

[redacted]

11.3 Regulatory Documentation

11.3.1 Institutional Review Board

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the IRB for written approval. A copy of the written approval of the protocol and informed consent form must be received by Blaze Bioscience before recruitment of subjects into the study and shipment of investigational products. Approval from the IRB must be obtained before starting the study and should be documented in a letter to the investigator specifying the protocol number and version and the date on which the IRB met and granted the approval.

Any modifications made to the protocol and/or informed consent form after receipt of IRB approval must also be submitted by the investigator to the IRB in accordance with institutional procedures and regulatory requirements.

11.3.2 Audits and Inspections

An audit is a systematic and independent examination of trial related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, standard operating procedures (SOPs) of Blaze Bioscience and/or its representatives or designees, GCP, and applicable regulatory requirement(s).

Authorized representatives of Blaze Bioscience, its designee, a regulatory authority, or the IRB may visit the center to perform audits or inspections. The investigator should contact Blaze Bioscience immediately if they are contacted by a regulatory agency about an inspection at their

center. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and allocate their time and the time of their staff to the auditor/inspector to discuss findings and any relevant issues.

11.3.3 Training

Study teams at the clinical sites will be trained on all aspects of the study.

Training will be conducted at the study initiation visits with the study coordinators, pharmacists, and investigators as well as at a central investigator meeting and in pre-scheduled webinars.

The study teams will be trained on the protocol evaluations, safety reporting, investigator brochure, informed consent, CRFs, pharmacy procedures, dosing, receipt and storage of tozuleristide, [redacted], inclusion and exclusion criteria, study manual, investigator responsibilities, GCP, [redacted] and data entry into the clinical database.

Every site's imaging operators and neurosurgeons will also receive specialized training in operating the Canvas system and image acquisition and interpretation including the following:

- Instructions on specimen flow in the Operating room and labeling of imaged specimens
- [redacted]
- Operation of the Canvas system including pitfalls and recognition of problems
- [redacted]
- Assessment of fluorescence intraoperatively
- Image and video capture and storage of data

[redacted]

11.3.4 Monitoring the Study

In accordance with ICH GCP guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the data recorded in the CRFs for consistency.

The study monitor, as a Blaze Bioscience representative, will contact and visit the investigator regularly and that he/she will be allowed, on request, to inspect the various records of the trial (CRFs and other pertinent data) provided that subject confidentiality is maintained in accord with local requirements.

It will be the monitor's responsibility to monitor the CRFs at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The investigator agrees to allow the monitor direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the monitor to discuss findings and any relevant issues.

11.3.5 Conditions for Modifying the Protocol

Site-requested protocol modifications which alter the scope of the investigation, the scientific quality of the study, the experimental design, dosages, duration of therapy, assessment variables, the number of subjects treated, or subject selection criteria, may be made after the review and approval of Blaze Bioscience.

All protocol modifications must be submitted to the IRB and responsible regulatory authority in accordance with local requirements. Approval must be awaited before significant changes can be

implemented except when necessary to eliminate immediate hazards to patients; i.e., if the risk benefit ratio is affected and/or the modification represents a change in basic trial definitions such as objectives, design, and sample size or outcome measures.

In the event of a SAE or AE, the investigator may institute any medical procedures deemed appropriate. Administrative changes to the protocol are defined as minor corrections and/or clarifications that have no effect on the way the study is to be conducted or on the safety of the subjects. These administrative changes will be agreed upon by Blaze Bioscience and the investigator and submitted to the IRB.

11.3.6 Conditions for Terminating the Study

The study may be prematurely terminated by the IRB or relevant regulatory authorities if the perception of the benefit/risk becomes unfavorable for continuation of the study. Additionally, Blaze Bioscience reserves the right to terminate the study at any time on the basis of new information regarding safety or efficacy, or if study progress is unsatisfactory, or for other administrative or commercial reasons.

[redacted]

Should this be necessary, the procedures will be arranged on an individual study basis after review and consultation by all parties. In terminating the study, Blaze Bioscience and the investigators will ensure that adequate consideration is given to the protection of the subjects' interests. The investigator should promptly inform the subjects and ensure appropriate therapy and follow-up and inform the relevant regulatory authorities and the IRB. All delivered study materials must be collected and all CRFs completed to the extent possible.

11.3.7 Confidentiality of Trial Documents and Subject Records

The investigator must assure the subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. On CRFs or other documents submitted to the Sponsor, subjects should not be identified by their names, but by the subject's initials and an identification code. The investigator should keep a subject identification log showing codes, names, and addresses. Documents not for submission to Blaze Bioscience (e.g., subject's written consent forms, identification log), should be maintained by the investigator in strict confidence.

All information concerning the study treatment and the Sponsor Company and its operation, such as patent applications, formulae, manufacturing processes, basic scientific data, and material not previously published are considered confidential and shall remain the sole property of the Sponsor. The investigator agrees to use this information only in accomplishing the study and will not use it for any other purposes without written consent from the Sponsor.

11.3.8 Publication of Data and Protection of Trade Secrets

In accord with standard editorial and ethical practice, Blaze Bioscience will support publication of the data from this study.

[redacted]

REFERENCES

1. Barbagallo GM, Certo F, Heiss K, Albanese V. 5-ALA fluorescence-assisted surgery in pediatric brain tumors: report of three cases and review of the literature. *Br J Neurosurg.* 2014 Dec;28(6):750-4.
2. Basch E. The missing voice of patients in drug-safety reporting. N Engl J Med. 2010;362(10):865-869.
3. Basch E, Deal AM, Dueck AC, et al. Overall Survival Results of a Trial Assessing Patient-Reported Outcomes for Symptom Monitoring During Routine Cancer Treatment. JAMA 2017;318(2):197-198.
4. Beez T, Sarikaya-Seiwert S, Steiger HJ, Hänggi D. Fluorescence-guided surgery with 5-aminolevulinic acid for resection of brain tumors in children--a technical report. *Acta Neurochir (Wien).* 2014 Mar;156(3):597-604.
5. Brinkman, Tara M., et al. Long-Term Neurocognitive Functioning and Social Attainment in Adult Survivors of Pediatric CNS Tumors: Results From the St Jude Lifetime Cohort Study. *Journal of Clinical Oncology*. 2016;34(23):1358–1367.
6. Bull KS, et al. Child-Related Characteristics Predicting Subsequent Health-Related Quality of Life in 8- to 14-Year-Old Children with and without Cerebellar Tumors: a Prospective Longitudinal Study. *Neuro-Oncology Practice*. Nov 2014;1(3):114–122.
7. Chi SN, Zimmerman MA, Yao X, Cohen KJ, Burger P, Biegel JA, Rorke-Adams LB, Fisher MJ, Janss A, Mazewski C, Goldman S, Manley PE, Bowers DC, Bendel A, Rubin J, Turner CD, Marcus KJ, Goumnerova L, Ullrich NJ, Kieran MW. Intensive multimodality treatment for children with newly diagnosed CNS atypical teratoid rhabdoid tumor. *J Clin Oncol.* 2009 Jan20;27(3):385-9.
8. Deshane J, Garner CC, Sontheimer H. Chlorotoxin inhibits glioma cell invasion via matrix metalloproteinase-2. *J Biol Chem*. 2003;278(6): 4135-4144.
9. Duckworth J, Nayiager T, Pullenayegum E, et al. Health-related quality of life in long-term survivors of brain tumors in childhood and adolescence: A serial study spanning a decade. *J Pediatr Hematol Oncol*. 2015;37(5):362–367.
10. Fisher PG, Tihan T, Goldthwaite PT, Wharam MD, Carson BS, Weingart JD, Repka MX, Cohen KJ, Burger PC. Outcome analysis of childhood low-grade astrocytomas. *Pediatr Blood Cancer.* 2008 Aug;51(2):245-50.
11. Gajjar A, Packer RJ, Foreman NK, Cohen K, Haas-Kogan D, Merchant TE; COG Brain Tumor Committee. Children's Oncology Group's 2013 Blueprint for Research: Central Nervous System Tumors. *Pediatr Blood Cancer*. 2013;60(6):1022-6.
12. Gurney, JG, et al. Social Outcomes in the Childhood Cancer Survivor Study Cohort. *Journal of Clinical Oncology*. Oct 2009;27(14):2390–2395.
13. Hervey-Jumper SL, Berger MS. Role of surgical resection in low- and high-grade gliomas. *Curr Treat Options Neurol*. 2015 Apr;16(4):284.
14. Huang T, Mueller S, Rutkowski MJ, Han SJ, Bloch O, Barani IJ, Parsa AT, Chang SM. Multidisciplinary care of patients with brain tumors. *Surg Oncol Clin N Am*. 2013;22(2):161-78.
15. Jakacki RI, Burger PC, Kocak M, Boyett JM, Goldwein J, Mehta M, Packer RJ, Tarbell NJ, Pollack IF. Outcome and prognostic factors for children with supratentorial primitive neuroectodermal tumors treated with carboplatin during radiotherapy: a report from the Children's Oncology Group. *Pediatr Blood Cancer.* 2015 May;62(5):776-83.
16. Kirch R, Reaman G, Feudtner C, Wiener L, Schwartz LA, Sung L, et al. Advancing a comprehensive cancer care agenda for children and their families: institute of Medicine Workshop highlights and next steps. CA Cancer J Clin. 2016;66(5):398–407.
17. Kotronoulas G, Kearney N, Maguire R, et al. What is the value of the routine use of patient-reported outcome measures toward improvement of patient outcomes, processes of care, and health service outcomes in cancer care? A systematic review of controlled trials. *J Clin Oncol.* 2014;32(14):1480-1501.

18. Kesavan K, Ratliff J, Johnson EW, et al. Annexin A2 is a molecular target for TM601, a peptide with tumor-targeting and anti-angiogenic effects. *J Biol Chem*. 2010;285(7):4366–74.
19. Kuhlthau KA, et al. Prospective Study of Health-Related Quality of Life for Children With Brain Tumors Treated With Proton Radiotherapy. *Journal of Clinical Oncology*. Oct 2012;30(17):2079–2086.
20. Pollack IF, Gerszten PC, Martinez AJ, Lo KH, Shultz B, Albright AL, Janosky J, Deutsch M. Intracranial ependymomas of childhood: long-term outcome and prognostic factors. *Neurosurgery*. 1995;37(4):655-57.
21. Robertson PL. Advances in treatment of pediatric brain tumors. *NeuroRx*. 2006;3(2):276-91.
22. Rogers L, Pueschel J, Spetzler R, Shapiro W, Coons S, Thomas T, Speiser B. Is gross-total resection sufficient treatment for posterior fossa ependymomas? *J Neurosurg.* 2005 Apr 102(4): 629-36.
23. Schulte F, Russell KB, Cullen P, Embry L, Fay-Mcclymont T, et al. Systematic review and meta-analysis of health-related quality of life in pediatric CNS tumor survivors. *Pediatric Blood & Cancer*. 2017;64(8).
24. Sievert AJ, Fisher MJ. Pediatric low-grade gliomas. *J Child Neurol*. 2009;24(11):1397-408.
25. Stroud MR, Hansen SJ, Olson JM. In vivo bio-imaging using chlorotoxin-based conjugates. *Curr Pharm Des*. 2011;17:4362–71.
26. Stummer W, Pichlmeier U, Meinel T, Wiestler OD, Zanella F, Reulen HJ; ALA-Glioma Study Group. Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. *Lancet Oncol.* 2006 May;7(5):392-401.
27. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, Belanger K, Brandes AA, Marosi C, Bogdahn U, Curschmann J, Janzer RC, Ludwin SK, Gorlia T, Allgeier A, Lacombe D, Cairncross JG, Eisenhauer E, Mirimanoff RO; European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups.; National Cancer Institute of Canada Clinical Trials Group. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N *Engl J Med.* 2005 Mar 10;352(10):987-96.
28. Tabori U, Laberge AM, Ellezam B, Carret AS. Cancer Predisposition in Children with Brain Tumors. In: Scheinemann K., Bouffet E. (eds) *Pediatric Neuro-oncology*. 2015;69-89.
29. U.S. Cancer Statistics Working Group. United States Cancer Statistics: 1999–2012 Incidence and Mortality Web-based Report. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; 2015. Available at: www.cdc.gov/uscs.
30. US DHHS, FDA. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance. Health Qual Life Outcomes. 2006; 4:79.
31. Veiseh M, Gabikian P, Bahrami SB, Veiseh O, Zhang M, Hackman RC, et al. Tumor paint: a chlorotoxin:Cy5.5 bioconjugate for intraoperative visualization of cancer foci. *Cancer Res.* 2007;67(14):6882–8.
32. Yang T, Temkin N, Barber J, Geyer JR, Leary S, Browd S, Ojemann JG, Ellenbogen RG. Gross total resection correlates with long-term survival in pediatric patients with glioblastoma. *World Neurosurg.* 2013 Mar-Apr;79(3-4):537-44.
33. Zeltzer PM, Boyett JM, Finlay JL, Albright AL, Rorke LB, Milstein JM, Allen JC, Stevens KR, Stanley P, Li H, Wisoff JH, Geyer JR, McGuire-Cullen P, Stehbens JA, Shurin SB, Packer RJ. Metastasis stage, adjuvant treatment, and residual tumor are prognostic factors for medulloblastoma in children: conclusions from the Children's Cancer Group 921 randomized phase III study. *J Clin Oncol.* 1999 Mar;17(3):832-45.
34. Zhao S, Wu J, Wang C, Liu H, Dong X, Shi C, Shi C, Liu Y, Teng L, Han D, Chen X, Yang G, Wang L, Shen C, Li H. Intraoperative fluorescence-guided resection of high-grade malignant gliomas using 5-aminolevulinic acid-induced porphyrins: a systematic review and meta-analysis of prospective studies. *PLoS One.* 2013 May 28;8(5):e63682.

APPENDIX A: PERFORMANCE STATUS CRITERIA

Karnofsky		**Lansky**	
Score	Description	Score	Description
100	Normal, no complaints, no evidence of disease	100	Fully active, normal.
90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly
70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
60	Required occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

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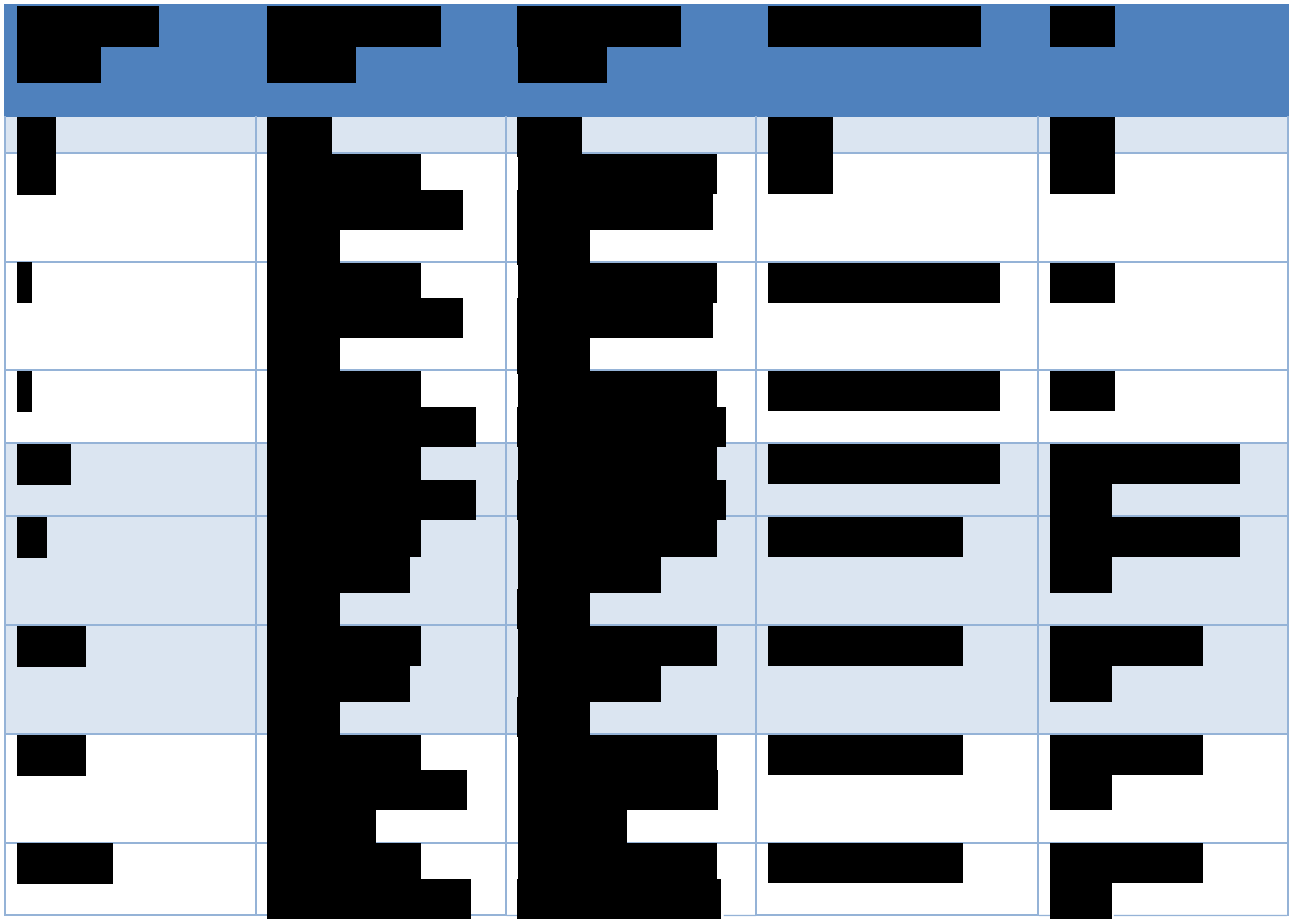

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