Protocol Title: A Phase 2/3 Randomized, Open-Label Study of Toca 511, a Retroviral Replicating Vector, Combined With Toca FC versus Standard of Care in Subjects Undergoing Planned Resection for Recurrent Glioblastoma or Anaplastic Astrocytoma

Protocol Number: Tg 511-15-01

EudraCT Number: 2015-004010-20

Study Sponsor: Tocagen Inc.
3030 Bunker Hill Street, Suite 230
San Diego, CA 92109
USA

Protocol Version: 6

Date: 18 October 2017

STATEMENT OF CONFIDENTIALITY

SPONSOR SIGNATURE

Sponsor Signatory: Asha Das, MD
Phone: (+) 1-858-412-8468
Fax: (+) 1-858-412-8499

This trial will be conducted in accordance with the ethical principles of Good Clinical Practice, per ICH Guideline E6.

Sponsor's Responsible Medical Officer:

{See appended electronic signature page}

Signature

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for vocimagene amiretrorepvec and flucytosine extended-release tablets, Toca 511 and Toca FC. I have read this protocol, Tg 511-15-01, and agree to conduct the study as outlined, and in accordance with Good Clinical Practice Guidelines (ICH E6) and the Clinical Trial Agreement.

I agree to maintain the confidentiality of all information received or developed in connection with this protocol and to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

_____
Printed Name of Investigator

_____
Signature of Investigator

_____
Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address, Email and Telephone Number
Medical Monitor	Justine Walker, MD	Address: 3030 Bunker Hill St., Suite 230 San Diego, CA 92109 Direct Phone: (+) 1-858-412-8445 Cell Phone: (+) 1-310-975-9226 Email: jwalker@tocagen.com
Drug Safety Physician	Tocagen Drug Safety	SAE Email: safety@tocagen.com SAE Facsimile: (+) 1-858-412-8454
24-Hour Emergency Contact	Medical Monitor	(+) 1-310-975-9226

2. SYNOPSIS

Name of Sponsor/Company: Tocagen Inc

Name of Investigational Product:

Toca 511 (vocimagene amiretrorepvec), a retroviral replicating vector (RRV) expressing a yeast-derived, codon-optimized cytosine deaminase (CD) prodrug-activator gene, in combination with Toca FC (flucytosine) extended-release tablets

Title of Study:

A Phase 2/3 Randomized, Open-Label Study of Toca 511, a Retroviral Replicating Vector, Combined With Toca FC versus Standard of Care in Subjects Undergoing Planned Resection for Recurrent Glioblastoma or Anaplastic Astrocytoma

Study Center(s):

Approximately 80 sites globally

Studied Period (years):	**Phase of Development:**
Date first patient enrolled: 11 November 2015 Estimated primary completion date: 30 December 2019 Estimated date last patient completed: 01 March 2023	2/3

Objectives:

Primary Objective:

To compare the overall survival (OS) of subjects treated with Toca 511 combined with Toca FC to subjects treated according to standard of care after tumor resection for recurrence of glioblastoma or anaplastic astrocytoma.

Secondary Objectives:

1. To evaluate the safety of each arm as administered in this study
2. To compare the durable response rate (DRR: CR or PR $\geq$ 24 weeks) between arms
3. To compare the durable clinical benefit rate (DCBR: CR or PR $\geq$ 24 weeks or SD $\geq$ 18 months) between arms
4. To assess the duration of durable response (DDR) of each arm
5. To assess OS and DRR by IDH1 mutation status
6. To compare overall survival at 12 months (OS12) between arms
7. To compare the patient reported outcome and quality of life between arms
8. To compare progression-free survival (PFS) rate at 12, 18, and 24 months between arms

Methodology:

This is a multicenter, randomized, open-label study of Toca 511 and Toca FC versus standard of care (SOC) that comprises Investigator's choice of either single agent chemotherapy (lomustine or temozolomide) or bevacizumab administered to subjects undergoing resection for first or second recurrence (including this recurrence) of glioblastoma or anaplastic astrocytoma. Subjects will be randomized at the time of surgery in a 1:1 ratio to receive either Toca 511 and Toca FC or control. Stratification will be done by IDH1 mutation (present or absent), by Karnofsky performance status (KPS [70-80 vs 90-100]) and by geographical region (United States, Canada, Ex-North America).

All subjects will have a Gd-MRI scan 24 to 48 hours after the resection for recurrent disease and a baseline scan prior to initiating Toca FC, chemotherapy, or bevacizumab. Repeat scans will be obtained every 6 weeks for the first year and every 3 months after that until EOT; thereafter, MRI scans will be collected per the institution's standard of care.

Subjects may receive any standard of care treatment after EOT. Crossover to the experimental arm is not allowed, unless the primary endpoints have been met and the Sponsor notifies the sites.

An Independent Data Monitoring Committee (IDMC) will be convened to review safety data on a periodic basis and to review interim efficacy analyses data as planned.

Number of Subjects (Planned):

Approximately 380 subjects

Diagnosis and Main Criteria for Inclusion:

Subjects undergoing resection for first or second recurrence (including this recurrence) of glioblastoma or anaplastic astrocytoma.

Subject Inclusion Criteria:

Each subject must meet all of the following inclusion criteria to be eligible for study entry:

1. Subject has given written informed consent
2. Subject is between 18 years old and 75 years old, inclusive
3. Subjects must have histologically proven GBM or AA and:
    a. Must have received first-line multimodal therapy with surgery followed by temozolomide (unless known MGMT promoter unmethylated) and radiation (subjects with GBM must have received temozolomide and radiation concurrently)
    b. Must be in first or second recurrence (including this recurrence)
    c. Recurrence must be confirmed by diagnostic biopsy with local pathology review or contrast-enhanced MRI. If first recurrence of GBM is documented by MRI, an interval of at least 12 weeks after the end of prior radiation therapy is required unless there is either: i) histopathologic confirmation of recurrent tumor, or ii) new enhancement on MRI outside of the radiotherapy treatment field
4. Subjects must have measurable disease preoperatively, defined as at least 1 contrast-enhancing lesion, with 2 perpendicular measurements of at least 1 cm, as per RANO criteria.

5. Subjects must be at least 4 weeks post last dose of temozolomide
6. Prior gamma knife, stereotactic radiosurgery, or other focal high-dose radiotherapy is allowed but the subject must have either histopathologic confirmation of recurrent tumor, or new enhancement on MRI outside of the radiotherapy treatment field
7. Based on the pre-operative evaluation by neurosurgeon, the subject is a candidate for ≥ 80% resection of enhancing region
8. IDH1 mutation status of the primary tumor must be available or tumor samples must be available for pre-randomization testing
9. Laboratory values adequate for patient to undergo surgery, including:
    a. Platelet count ≥ 60,000/mm^3
    b. Hgb ≥ 10 g/dL
    c. Absolute neutrophil count (ANC) ≥ 1,500/mm^3
    d. Absolute lymphocyte count (ALC) ≥ 500/mm^3
    e. Adequate liver function, including:
        - Total bilirubin ≤ 1.5 x ULN (unless has Gilbert's syndrome)
        - ALT ≤ 2.5 x ULN
    f. Estimated glomerular filtration rate of at least 50 mL/min by the Cockcroft Gault formula below:

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times [0.85 \; if \; Female]}{72 \times \text{Serum Creatinine (in mg/dL)}}$$

10. Women of childbearing potential (women who have not had ≥12 months of non-therapy-induced amenorrhea or are not surgically sterile) must have had a negative serum pregnancy test within the past 21 days and must use a birth control method in addition to barrier methods (condoms).
11. Subject or subject's partner is willing to use condoms for 12 months after receiving Toca 511 or until there is no evidence of the virus in the subject's blood, whichever is longer.
12. The subject has a KPS ≥ 70
13. The subject is willing and able to abide by the protocol

Subject Exclusion Criteria:

1. History of more than 2 prior recurrences (including this recurrence) of GBM or AA
2. History of other malignancy, unless the patient has been disease-free for at least 5 years. Adequately treated basal cell carcinoma or squamous cell skin cancer is acceptable regardless of time, as well as localized prostate carcinoma or cervical carcinoma in situ after curative treatment
3. Histologically confirmed oligodendroglioma or mixed glioma
4. Known 1p/19q co-deletion

5. A contrast-enhancing brain tumor that is any of the following:
    a. Multi-focal (defined as 2 separate areas of contrast enhancement measuring at least 1 cm in 2 planes that are not contiguous on either fluid-attenuated inversion recovery (FLAIR) or T2 sequences);
    b. Associated with either diffuse subependymal or leptomeningeal dissemination; or
    c. > 5 cm in any dimension
6. The subject has or had any active infection requiring systemic antibiotic, antifungal or antiviral therapy within the past 4 weeks
7. The subject has any bleeding diathesis, or must take anticoagulants, or antiplatelet agents, including nonsteroidal anti-inflammatory drugs (NSAIDs), at the time of the scheduled resection that cannot be stopped for surgery
8. The subject is human immunodeficiency virus (HIV) positive
9. The subject has a history of allergy or intolerance to flucytosine
10. The subject has a gastrointestinal disease that would prevent him or her from being able to swallow or absorb flucytosine
11. The subject received cytotoxic chemotherapy within the past 4 weeks (6 weeks for nitrosoureas) of the planned surgery date
12. The subject received any investigational treatment within the past 30 days or prior immunotherapy or antibody therapy within the past 45 days.
13. The subject is pregnant or breast feeding
14. The subject intends to undergo treatment with the Gliadel® wafer at the time of this surgery or has received the Gliadel® wafer < 30 days from W1D1 (surgery)
15. The subject has received bevacizumab for their disease unless in the context of primary therapy for newly diagnosed glioma
16. For subjects planned to potentially receive bevacizumab, they have no evidence of uncontrolled hypertension (defined as a blood pressure of ≥ 150 mm Hg systolic and/or ≥ 100 mm Hg diastolic on medication) or active GI perforation
17. The subject has received systemic dexamethasone continuously at a dose > 8 mg/day for 8 weeks prior to the date of the screening assessment
18. Severe pulmonary, cardiac or other systemic disease, specifically:
    - New York Heart Association > Grade 2 congestive heart failure within 6 months prior to study entry, unless asymptomatic and well controlled with medication (see Appendix F)
    - Uncontrolled or significant cardiovascular disease, clinically significant ventricular arrhythmia (such as ventricular tachycardia, ventricular fibrillation, or Torsades des pointes), clinically significant pulmonary disease (such as ≥ Grade 2 dyspnea, according to CTCAE 4.03)

- Subjects who have any other disease, either metabolic or psychological, which as per Investigator assessment may affect the subject's compliance or place the subject at higher risk of potential treatment complications

Investigational Product, Dosage and Mode of Administration:

Toca 511: Tumor resection, followed by 4 mL of Toca 511 injected into the wall of the resection cavity

Toca FC: Beginning approximately 6 weeks after tumor resection, subjects will begin the first cycle with a 7-day course of oral Toca FC dosed at 220 mg/kg/day, and repeated approximately every 6 weeks

Duration of Treatment:

Toca 511 will only be administered once during this study. Toca FC will be taken by the subject as long as the drug is tolerated and the investigator believes the subject may be obtaining benefit. SOC will be taken by the subject until confirmed progression or End of Treatment (see Section 8.3).

Reference Therapy, Dosage and Mode of Administration:

- Lomustine as a single oral dose of 110 mg/m^2 repeated every 6 weeks

  or
- Temozolomide either at a dose of 50 mg/m^2 once daily continuously

  or
- Temozolomide at an initial dose of 150 mg/m^2 once daily for 5 consecutive days per 28-day treatment cycle that may be raised to 200 mg/m^2 once daily for 5 consecutive days in the following 28-day treatment cycles

  or
- Bevacizumab at 10 mg/kg by intravenous (IV) infusion every 2 weeks

Criteria for Evaluation:

Efficacy:

- Overall survival – time from randomization date to death due to any cause
- Durable response rate – the proportion of subjects whose best overall response is either CR or PR lasting at least 24 weeks, according to modified RANO criteria as assessed by IRR, in addition to clinical status and steroid use
- Duration of durable response – time from documentation of durable response to disease progression or death due to disease progression
- Durable clinical benefit rate – the proportion of subjects whose best overall response is either CR or PR lasting at least 24 weeks, or stable disease (SD) lasting at least 18 months, according to modified RANO criteria as assessed by IRR, as well as clinical status and steroid use
- Progression-free survival – time from randomization date to tumor progression based on modified RANO criteria as assessed by an independent radiology review (IRR) or death due to any cause, as well as clinical status and steroid use

- Patient reported outcome – as assessed by the EQ-5D-5L, the EORTC QLQ-C30, and the EORTC QLQ-BN20

Safety:

- Safety – includes analysis of all adverse events, serious adverse events (both related and all causality), and assessment of laboratory shift tables. In addition, there will be periodic reviews by an IDMC.

Statistical Methods:

The assumed median OS for subjects in the control arm is 9.8 months (Reardon 2017), and the median OS for subjects in the Toca 511 and Toca FC arm is 14.3 months (based on preliminary Phase 1 data). With an assumed active enrollment duration of 28 months and an additional 18 months of follow-up, a sample size of approximately 380 subjects in total is planned to achieve the required number of 257 OS events (deaths) to detect a hazard ratio (HR) of 0.685 at a two-sided alpha of 0.05 and a power of 85%.

Two interim analyses and one final analysis are planned for OS. It is anticipated that at the time of the first interim analysis all 380 subjects would have been randomized into the study.

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

LIST OF TABLES

LIST OF FIGURES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol:

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AA	anaplastic astrocytoma
AG	astroglioma
AE	adverse event
ALT	alanine aminotransferase
AOA	anaplastic oligoastrocytoma
AOD	anaplastic oligodendroglimas
AST	aspartate aminotransferase
ATRX	alpha thalassemia/mental retardation syndrome X-linked
BID	twice daily dosing
BLOQ	below limit of quantification
BSL-2	Biosafety Level 2
BUN	blood urea nitrogen
CBC	complete blood count
CBR	clinical benefit rate
CD	cytosine deaminase
CFR	Code of Federal Regulations
CR	complete response
CRF	case report form
CGD	chronic granulomatous disease
CSF	cerebrospinal fluid
CTCAE	Common Toxicity Criteria Adverse Events
DCBR	durable clinical benefit rate
DOR	duration of response
DRR	durable response rate
EDC	electronic data capture
EOT	end of treatment (for the purpose of this study, at the time of confirmed progression, regardless of continuation of treatment)
EOS	end of study

Abbreviation or Specialist Term	Explanation
5-FC	5-fluorocytosine, flucytosine
5-FU	5-fluorouracil
FDA	Food and Drug Administration
GBM	glioblastoma multiforme
GCP	Good Clinical Practice
Gd-MRI	gadolinium-enhanced MRI scan
GFR	glomerular filtration rate
HGG	high grade glioma
HIPAA	Health Insurance Portability and Accountability Act
HR	hazard ratio
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ID	identification
IDH	isocitrate dehydrogenase
IEC	Independent Ethics Committee
IDMC	Independent Data Monitoring Committee
IRB	Institutional Review Board
IRR	independent radiology review
ITT	intent-to-treat (population)
IV	intravenous
Kg	kilogram
KPS	Karnofsky Performance Score
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MGMT	O6-methylguanine-DNA methyltransferase
mg	milligram
mL	milliliter
MLV	murine leukemia virus
mOS	median overall survival
MRI	magnetic resonance imaging
NSAID	nonsteroidal anti-inflammatory
NCI	National Cancer Institute

Abbreviation or Specialist Term	Explanation
OR	operating room
ORR	objective response rate
OS	overall survival
OS9	overall survival at 9 months
OS12	overall survival at 12 months
OS18	overall survival at 18 months
OS24	overall survival at 24 months
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PFS	progression-free survival
PI	Principal Investigator
PO	oral (administration)
qPCR	quantitative polymerase chain reaction
qRT-PCR	reverse transcriptase quantitative polymerase chain reaction
RANO	Response Assessment in Neuro-Oncology Working Group
RG-2	Risk Group 2
RRV	retroviral replicating vector
SAE	serious adverse event
SAP	statistical analysis plan
SCID-X1	X-linked severe combined immunodeficiency
SD	stable disease
SOC	standard of care
SOE	Schedule of Events
TEAE	treatment-emergent adverse events
Toca 511	RRV containing modified yeast cytosine deaminase transgene
Toca FC	5-fluorocytosine, 5-FC, flucytosine extended-release tablets
TU	transducing units
ULN	upper limit of normal
VEGF	vascular endothelial growth factor
WAS	Wiskott-Aldrich syndrome
WHO-DD	World Health Organization Drug Dictionary
yCD2	modified yeast cytosine deaminase gene

5. INTRODUCTION

5.1. Malignant Gliomas

Malignant gliomas account for approximately 70% of the 23,000 new cases of malignant, primary brain tumors diagnosed in adults in the United States (US) each year. The worldwide incidence rate of malignant glioma is approximately 3-5/100,000 individuals, for an overall estimated total of 256,000 cases (CBTRUS Fact Sheet 2014). Glioblastomas (GBM) account for approximately 60 to 70% of malignant gliomas, anaplastic astrocytomas (AA) for 10 to 15% and anaplastic oligodendrogliomas (AOD) and anaplastic oligoastrocytomas (AOA) for about 10% (Wen 2008). Glioblastoma, and to a somewhat lesser extent, the other tumor types listed above, are biologically aggressive tumors that present unique treatment challenges due to the following characteristics: 1) location in or near vital or eloquent areas of the brain, 2) intrinsic resistance to conventional therapies, 3) limited capacity of the brain for self-repair, 4) propensity for the tumor to infiltrate surrounding normal brain tissue, 5) variable and unpredictable interference with drug delivery by the blood brain barrier, and 6) tumor capillary leakage with resultant peritumoral edema and intracranial hypertension (Chamberlain 2006).

The current standard of care (SOC) for newly diagnosed high grade glioma (HGG) has evolved to include maximum safe extent resection plus conventionally fractionated external beam radiotherapy with concurrent administration of the alkylating agent temozolomide. Temozolomide is an orally active alkylating agent approved for treatment of GBM in several countries. The combination of temozolomide and radiation following surgery was associated with a significant increase in median progression-free survival (PFS) (5 vs. 6.9 months) and overall survival (OS; 12.1 vs. 14.6 months) compared to radiation alone (Stupp 2005). However, as these results demonstrate, the overall prognosis for this disease remains poor and underscores the need for better therapies (Chamberlain 2006).

Despite aggressive treatment, nearly all malignant gliomas eventually recur. For recurrent GBM, the median PFS is as short as 1.8 months (Ballman 2007). Chemotherapy shows moderate benefit in recurrent anaplastic gliomas, but is of limited benefit in treating recurrent GBM (Wen 2008, Wick 2010, Batchelor 2013, Taal 2014). Outcomes are summarized in Table 3.

Table 3: Clinical Trials in Recurrent Glioblastoma

Reference	Study Design	Population	mOS (months)
Batchelor 2013	Phase 3 study of cediranib vs lomustine	GBM, first recurrence, N = 65	9.8
Taal 2014	Randomized Phase 2 of lomustine vs bevacizumab vs combination	GBM, first recurrence, no prior bevacizumab, surgery for recurrence in 13%, N = 46	8
Wick 2010	Phase 3 study of enzastaurin vs lomustine	GBM, first and second recurrence N = 92	7.1

In addition to nitrosoureas such as lomustine, temozolomide has been used as monotherapy for recurrent GBM (Weller 2013). In recurrent GBM after adjuvant temozolomide, median OS (mOS) with continuous dose-intense temozolomide was 9.3 months (Perry 2010). Bevacizumab, a humanized monoclonal antibody against VEGF, was granted accelerated approval by the US Food and Drug Administration (FDA) as a single agent for the treatment of recurrent GBM. The observed response rate was 28% with a mOS of 9.2 months (Friedman 2009, Avastin® US Prescribing Information). However, the European Medicines Agency (EMA) rejected this indication. For this reason, bevacizumab is being used as the standard treatment for recurrent GBM in the United States but not in Europe.

The impact of isocitrate dehydrogenase (IDH) mutational status as a prognostic factor for AA and a subset of secondary GBM has been confirmed (Shibahara 2015). Thus, IDH mutational status is one stratification factor in this trial to ensure balance across both arms. MGMT methylation status is a clear prognostic factor in newly diagnosed GBM (Hegi 2005). Given the difficulty of performing this assay consistently and that about 20-30% of patients cannot be classified, this test will be used for post-study stratification purposes.

Codeletion of chromosome arms 1p and 19q (1p/19q codeletion), occurs in less than 20% of patients with Grade II-IV gliomas (Eckel-Passow 2015). These patients may differ dramatically in life expectancy (Le Rhun 2015). Therefore, patients with a known1p/19q codeletion are excluded from this trial. Those patients with IDH mutations and no 1p19q codeletions are typically ATRX (alpha thalassemia/mental retardation syndrome X-linked) deleted (Shibahara 2015). The ATRX deleted patient subgroup have a favorable prognosis compared to IDH mutations without deletions, but the favorable survival advantage is much less compared to the 1p/19q deletions. Therefore, ATRX deleted patients are included in the study and will be randomized as part of the IDH mutation randomization.

Given the dismal outlook, there is an ongoing, intensive search for novel or targeted therapies to improve the prognosis of subjects with high grade gliomas. Gene transfer is one such approach. A review article by Kaufmann and Chiocca describes more than 30 ongoing or completed trials of gene therapy in subjects with malignant gliomas, using either replicating or non-replicating viruses (Kaufmann 2014). The non-replicating vector studies demonstrated that delivery of therapeutic genes to subjects with malignant gliomas is generally safe, but of limited efficacy due to failure to deliver the therapeutic gene to a significant portion of the tumor cells. Oncolytic replicating viruses have been generally well tolerated, but low frequency of durable efficacy has been demonstrated to date.

5.2. Introduction to Therapy and Background

Toca 511 (vocimagene amiretrorepvec), in combination with Toca FC (flucytosine) extended-release tablets, is an investigational combination product currently under development for the treatment of HGG. Toca 511 is a retroviral replicating vector (RRV) derived from a cloned Moloney murine leukemia virus (MLV). The original ecotropic envelope gene has been replaced with an amphotropic envelope gene, enabling the virus (referred to as ampho MLV) to infect human cells (Logg 2001). A modified yeast cytosine deaminase (CD) gene (yCD2) has been inserted into this vector (Perez 2012). The vector and CD gene construct is classified as a prodrug activator form of gene transfer, in which the prodrug-activator CD enzyme catalyzes the intracellular conversion of the antifungal drug, flucytosine (5-fluorocytosine [5-FC]), to the

antineoplastic drug 5-fluorouracil (5-FU). As an MLV-derived vector, Toca 511 is designed to selectively infect tumor cells, as MLV infects only actively dividing cells and viral replication is further restricted by innate and adaptive immune responses that are defective in malignant cells but intact in normal tissues (Ostertag 2012).

Tocagen is attempting to overcome the shortcomings of previous gene transfer protocols, by using the RRV to deliver the therapeutic gene, cytosine deaminase, to the tumor cells. This approach has the following advantages:

- Selectivity for transduction occurs because the retrovirus infects only dividing cells and is able to survive in the immune privileged cancer environment.
- The replicating virus stably integrates into the genome of the existing cancer cells and is passed to all future generations of tumor cells, and also produces progeny viruses which can infect other cancer cells. Together, this mechanism allows for multiple cycles of prodrug therapy, creating the potential for long-term tumor control.
- The virus is not intrinsically oncolytic and inside the tumor does not induce a host immune response significant enough to halt the infection process.
- The CD enzyme is capable of converting the prodrug 5-FC to the antineoplastic drug 5-FU. Since 5-FU is generated in the tumor and has a very short half-life, the toxicities seen with systemic administration of 5-FU are not anticipated. The 5-FU kills the infected and dividing cancer cells and diffuses to surrounding tumor cells and kills those which are dividing. Further, it may have an impact on immune-conversion by destroying immunosuppressive myeloid cells including myeloid derived immune-suppressive cells and thus reestablishing immunity to tumor.
- The combination of cyclic 5-FU induced tumor cell killing, expression of exogenous genes, presence of viral antigens, killing of immunosuppressive myeloid cells, and potentially other factors may induce immune mediated, anti-tumor responses.

Administration of Toca 511 and Toca FC has been shown to achieve long term survival benefits in both xenograft and syngeneic intracranial mouse tumor models (Ostertag 2012). In addition, Toca 511 and Toca FC combination treatment has shown encouraging evidence for increased survival in patients with high grade glioma, including glioblastoma, compared to historical controls, in early stage clinical studies. In addition, in these studies, tumor shrinkage, in some cases with complete disappearance of lesions, has been demonstrated based on independent radiology review.

5.2.1. Clinical Studies with Toca 511 and Toca FC

Subjects have been treated across three Phase 1 ascending dose studies of Toca 511 and Toca FC combination treatment in patients with recurrent HGG, conducted in the United States. In addition, a long-term follow-up study is ongoing for subjects that have previously been treated with Toca 511, to evaluate for delayed adverse events (AEs) in accordance with regulatory requirements for gene transfer studies.

The initial, first-in-human clinical study (Tg 511-08-01, NCT01156584) is an ascending dose study of the safety and tolerability of increasing doses of Toca 511 administered intratumorally, via stereotactic, transcranial injection and followed by orally administered Toca FC. This study showed that a single intratumoral administration of Toca 511 was both safe and well tolerated. Re-excision of tumor followed by analysis has revealed the presence of virus. In each case, the vector was detected at multiple sites in the recurrent brain tumor indicating that Toca 511 can survive and spread in these tumors.

The second clinical study (Tg 511-11-01, NCT01470794) is evaluating ascending doses of Toca 511 injected into the bed of the resection cavity in subjects with recurrent HGG who are undergoing resection, followed by orally administered Toca FC. The evaluation of subject survival is ongoing. To date, preliminary median OS is substantially prolonged in comparison to historical controls.

The third clinical study (Tg 511-13-01, NCT01985256) is evaluating the safety and tolerability of increasing doses of Toca 511 administered intravenously with subsequent intracranial delivery at the time of resection and followed by orally administered Toca FC, in subjects with recurrent HGG who are undergoing planned resection.

Patients on these Phase 1 trials who, in the opinion of the investigator, are receiving benefit from Toca FC may continue receiving therapy on a continuation study (Tg 511-09-01).

In the context of these trials, the combined dosing of Toca 511 and Toca FC has been evaluated and found to be safe. A common finding so far has been the encouraging safety profile of Toca 511 and Toca FC, with few reported related Grade 3 or higher adverse events. Refer to the Toca 511 and Toca FC Investigator's Brochure for detailed information, including relevant non-clinical data and clinical data from the studies described above.

5.3. Summary of Risks and Benefits

5.3.1. Potential Risks

Toca 511 is an investigational gene transfer product. In previous gene transfer trials involving intratumoral injections of other vectors for malignant gliomas, the following side effects have been noted: seizures, intratumoral hemorrhage, brain abscess, increased intracranial pressure, hydrocephalus, thromboembolic events, headache, fatigue, neurologic changes, pancytopenia, leukopenia, leukocytosis, and transiently increased liver enzymes (Kaufmann 2014, Murphy 2013).

As Toca 511 is a RRV, the risk of viral dissemination outside the tumor is a theoretical concern. Cohabitation studies in mice indicated no evidence of horizontal transmission of virus from highly viremic mice to naïve cage mates. In fact in nature, MLV is transferred predominantly through vertical transmission and has not been observed to naturally cross to other, even closely related, species. In laboratory dogs, there was no evidence of biodistribution, and virus was not detected in any shedding samples (blood, urine, feces, saliva and semen). Published studies of ampho MLV (similar to Toca 511) in primates have shown that the virus is rapidly cleared from the circulation in immunocompetent animals and does not cause disease. In primates, the presence of even minimal immune function controls infection and prevents disease (Cornetta 1990, Cornetta 1991). The current human clinical study contains inclusion and

exclusion criteria designed to exclude severely immune suppressed subjects from entering the study. Subjects will be screened at intervals during the trial for evidence of viral sequences in blood.

MLV can cause lymphoma in certain strains of mice. Lymphomas were observed at about 6 months after vector administration in BALB/c mice treated with Toca 511 administered intracranially or intravenously without subsequent administration of 5-FC. No lymphomas were observed when Toca 511 was administered at lower doses or when administration was followed by treatment with 5-FC. In the absence of findings in other target sites or in other species, the relevance of lymphoma in BALB/c mice to human carcinogenic risk is unknown (Wogan 1984).

In studies using nonreplicating vectors to treat subjects with inherited disorders of the immune system, human subjects have developed leukemia or other blood dyscrasias, for example in trials involving patients with X-linked Severe Combined Immunodeficiency (SCID-X1) and Wiskott-Aldrich syndrome (WAS) (Rans 2009, Hacein-Bey-Abina 2003, Braun 2014). Further, two of 10 subjects with chronic granulomatous disease (CGD) developed a myelodysplastic syndrome after gene transfer with a nonreplicating retroviral vector (Stein 2010). Each of these studies involved the ex vivo transduction of hematopoietic stem cells with subsequent cytokine-driven expansion of the transduced cell populations. In the SCID-X1 and the WAS cases, the subjects were infants or young children with immature immune systems and the transgene likely conferred a survival advantage on the transduced cells.

The risk of this type of virus associated oncogenesis occurring with Toca 511 is low, since its use does not involve ex vivo transduction of hematopoietic stem cells with subsequent cytokine-driven expansion and marrow conditioning with alkylating agents. In addition, the current protocols are treating adult patients who do not have immature immune systems or severe immunodeficiency. The CD gene expressed by Toca 511 has not been associated with any reports of carcinogenesis, nor is it known to confer a survival advantage on transduced cells in which it is expressed. More important, rather than expansion of the inserted gene as in the three studies mentioned above, the current cancer protocol involves the destruction of cells infected with the transgene. The importance of this difference seems to be confirmed by the observation that following administration of Toca 511 to mice, lymphomas were not seen in the groups that received subsequent treatment with 5-FC. For these reasons, the risk of lymphoma/leukemia in adults treated with Toca 511 is felt to be low. Further, large cohorts of humans have been exposed to MLV, as evidenced by widespread low-level antibody titers, without any evidence of secondary malignancy or, in fact, of any late toxicity.

Flucytosine is an orally available antifungal drug that crosses the blood brain barrier and that has been available since the 1970s to treat patients with fungal infections of the central nervous system (marketed in the US as Ancobon® and elsewhere as Ancotil®). The drug is generally well tolerated and safe when the peak serum concentration does not exceed 100 μg/mL for more than 2 weeks. In this trial, Toca FC will be administered for 7 days in each cycle. The known side effects of this drug include gastrointestinal intolerance (nausea, vomiting, and diarrhea), elevation of hepatic enzymes, and bone marrow suppression, all of which can usually be dealt with through dose reduction or possibly dosing interruption (Vermes 2000). An investigational extended-release formulation of flucytosine, Toca FC, is being used in the Toca 511 clinical studies. To date, minimal to no myelosuppression has been seen with Toca FC in the context of this regimen.

The prescribing information for Ancobon/Ancotil notes that flucytosine must be given with extreme caution to patients with impaired renal function. Since flucytosine is excreted primarily by the kidneys, renal impairment may lead to accumulation of the drug. Flucytosine must also be given with caution to patients with bone marrow depression. Patients may be more prone to depression of bone marrow function if they: 1) have a hematologic disease, 2) are being treated with radiation or drugs which depress bone marrow, or 3) have a history of treatment with such drugs or radiation. Bone marrow toxicity can be irreversible and may lead to death in immunosuppressed patients. Therefore, close monitoring of hematologic, renal, and hepatic status of all patients is essential while treating with Toca FC.

5.3.2. Potential Benefits

Preliminary survival analyses conducted on subjects enrolled in early stage clinical studies of Toca 511 and Toca FC combination therapy have indicated a potentially meaningful longer median OS when compared to published historical controls. Refer to the Investigator's Brochure for additional information.

Given the poor prognosis of the patient population and the lack of satisfying treatments to date, further evaluation of Toca 511 in combination with Toca FC is warranted.

5.4. Justification of the Dose, Schedule and Route of Administration of Toca 511

The Toca 511 doses studied in the first-in-human Phase 1 study, Tg 511-08-01, have ranged between 3.9×10^6 TU (transducing units) and 1.5×10^9 TU (intratumoral administration), and at all doses was well tolerated. In the surgical resection study, Tg 511-11-01, doses of Toca 511 up to 4.8×10^9 TU have been safely administered following removal of most of the tumor. A maximum tolerated dose was not identified in the Phase 1 clinical studies (Tg-511-08-01, Tg 511-11-01, and Tg 511-13-01). This study will use a volume of 4 mL (approximately 1.3×10^9 TU). This amount of virus is within the dose found safe and well tolerated in the previous studies.

Toca 511 will be administered by making multiple injections into the tumor bed immediately following resection. This method of administration has been utilized in prior gene transfer studies and has generally been found to be safe and well tolerated (Rainov 2000). A blunt-tipped, side-firing needle with centimeter markers to aid accurate depth of injection will be used (see Appendix C).

5.5. Justification of the Dose, Schedule, and Route of Administration of Toca FC

The Toca FC doses studied in the Phase 1 clinical studies have ranged from 120 mg/kg/day to 300 mg/kg/day, and at all doses was well tolerated. This study will use a dose of 220 mg/kg/day for 7-day courses of oral Toca FC to be repeated every 6 weeks.

Refer to the Investigator's Brochure for additional information regarding the justification of the route of administration and dosing for Toca FC.

5.6. Population to be Studied

This study will enroll approximately 380 subjects with GBM or AA whose tumor has recurred or progressed following first-line therapy. Subjects with known methylated MGMT promoter must have received first-line therapy with resection, followed by temozolomide and radiotherapy (given concurrently in subjects with GBM). All subjects with known unmethylated MGMT promoter must at least have received resection followed by radiation. Patients to be studied must have elected to undergo repeat resection.

6. TRIAL OBJECTIVES AND PURPOSE

6.1. Primary Objective

To compare the OS of all subjects treated with Toca 511 combined with Toca FC to subjects treated according to standard of care after tumor resection for recurrence of GBM or AA.

6.2. Secondary Objectives

1. To evaluate the safety of each arm as administered in this study
2. To compare the DRR (CR or PR ≥ 24 weeks) between arms
3. To compare the durable clinical benefit rate (DCBR: CR or PR ≥ 24 weeks or SD ≥ 18 months) between arms
4. To assess the duration of durable response (DDR) of each arm
5. To assess OS and DRR by IDH1 mutation status
6. To compare overall survival at 12 months (OS12) between arms
7. To compare the patient reported outcome and quality of life between arms
8. To compare progression-free survival (PFS) rate at 12, 18, and 24 months between arms

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a multicenter, randomized, open-label study of Toca 511 and Toca FC versus standard of care that comprises Investigator's choice of single agent chemotherapy (lomustine or temozolomide) or bevacizumab administered to subjects undergoing resection for first or second recurrence (including this recurrence) of GBM or AA. Subjects meeting all of the inclusion and none of the exclusion criteria will be randomized at the time of surgery in a 1:1 ratio to receive either Toca 511 and Toca FC (Experimental arm, Arm T) or control treatment with one option of standard of care (Arm SOC). Due to the prognostic influence of molecular subgroups such as IDH mutation, the trial will be stratified based on this determination from the primary pathology or subsequent biopsy known locally or otherwise determined centrally. A recent biopsy for this determination is not required for this study. A second stratification factor is based on the patient's Karnofsky Performance Score (KPS) (70-80 vs 90-100). Further, to account for potential differences in treatment choices for the control arm in regions, the trial will be stratified by geographical region (United States, Canada, ex-North America) during the randomization process.

7.2. Number of Subjects

Approximately 380 subjects will be randomized in this study.

7.3. Treatment Assignment

Subjects meeting all of the inclusion and none of the exclusion criteria will be randomized at the time of surgery in a 1:1 ratio to receive either Toca 511 and Toca FC or control treatment. The intent of randomizing at the time of surgery is to reduce potential bias and maintain the subject blind until after surgery. Those subjects who will undergo surgery after hours should be randomized as close to the time of surgery as possible.

The randomization code will be generated by a centralized randomization system, which will also be used to communicate subject randomizations to study sites. All randomized subjects will have both a unique subject identifier and a unique random code identifier. No random code identifiers are to be reused once assigned.

7.4. Investigator Choice

Since there are various treatment alternatives for recurrent GBM or AA, investigators may choose any of the single agent treatments for subjects randomized to the SOC arm listed in Table 4 for the control treatment arm. When selecting the treatment, investigators should take into consideration the subject's prior treatment (eg, subjects who had received prior lomustine should not receive it again) and clinical status following surgical resection of the tumor.

Table 4: Investigator's Choice Single Agent Treatments

Single Agent Treatment	Dose
Lomustine	(Oral [PO]) 110 mg/m^2 repeated every 6 weeks
Temozolomide	(PO or IV) Initial dose of 150 mg/m^2 once daily for 5 consecutive days per 28-day treatment cycle, may be increased to 200 mg/m^2 once daily for 5 consecutive days in the following 28-day treatment cycles
Temozolomide metronomic	(PO) 50 mg/m^2 once daily continuously
Bevacizumab	(IV) 10 mg/kg every two weeks

7.5. Study Duration and Follow-up

As per regulatory requirements for the monitoring of delayed adverse events in gene transfer trials, an attempt will be made to follow subjects who received Toca 511, as described in Table 11. In the event of early study termination by the Sponsor or Regulatory Authorities, an attempt will be made to continue long-term follow up for safety until death or for 15 years, whichever occurs first, in those subjects who have received Toca 511. All patients enrolled in the study will be followed for survival.

7.6. Criteria for Study Termination

The Sponsor or the Regulatory Authorities may decide to terminate the study at any time. Furthermore, the Sponsor will consider recommendations provided by the Independent Data Monitoring Committee (IDMC) with regards to study continuation, modification, and/or termination.

7.7. Study Schematic

Figure 1: Study Schematic

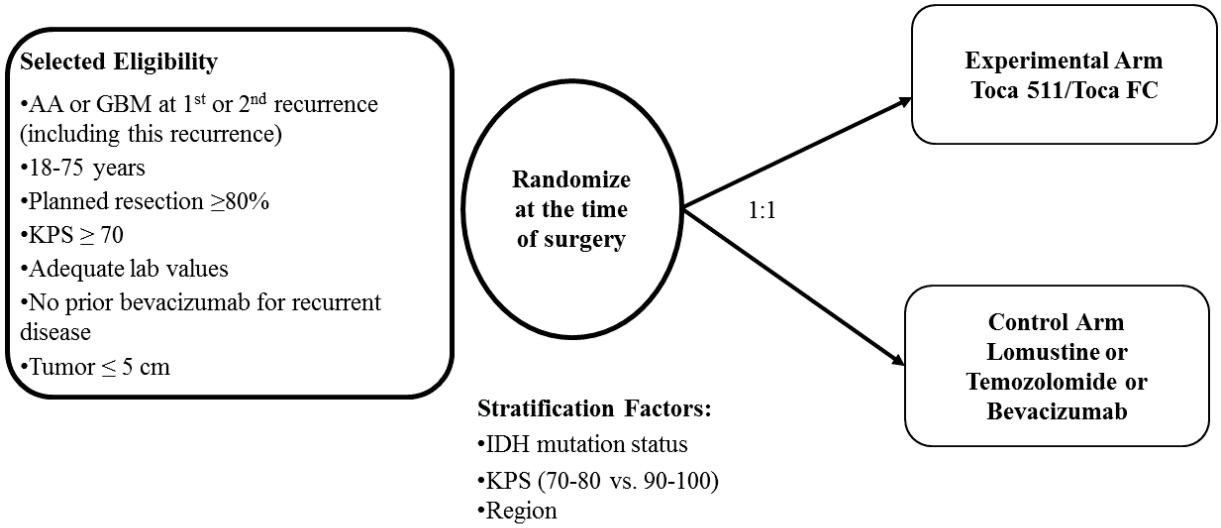
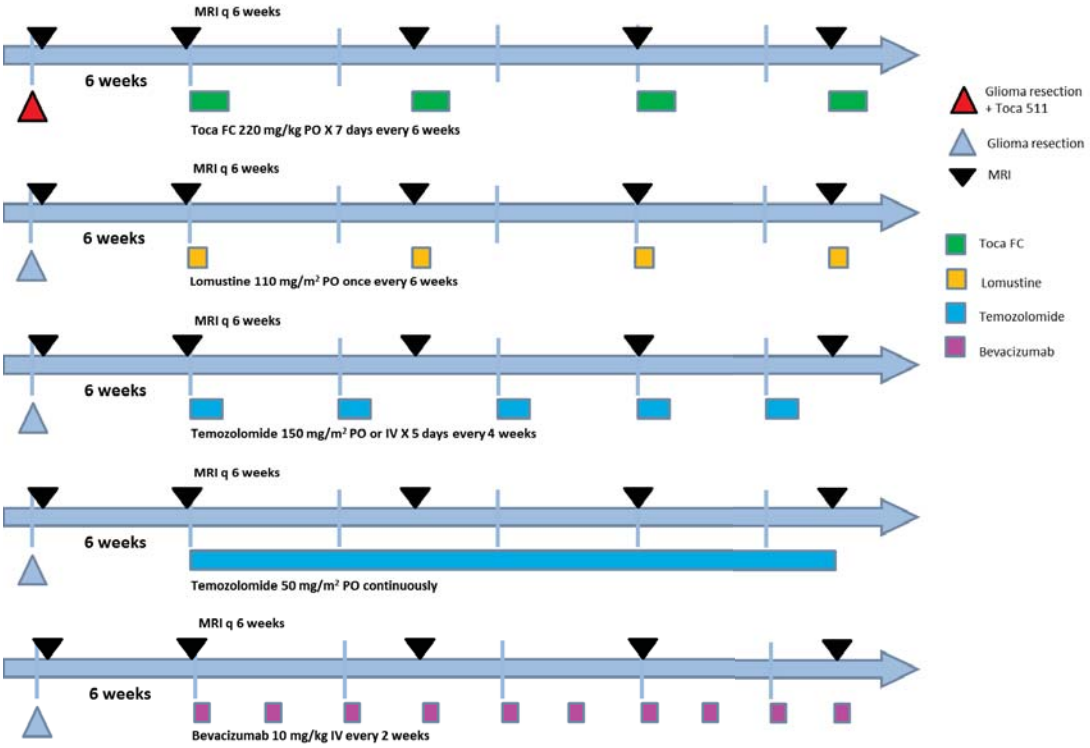


Figure 2: Schedule of Experimental Arm and the Control Arm Options

Systemic treatment in the Experimental arm and in the SOC arm will begin approximately 6 weeks after surgery, providing the subject has sufficiently recovered from surgery. Treatment may begin later than 6 weeks if the subject is considered unable to begin treatment due to their postoperative condition, ie, inability to swallow Toca FC or chemotherapy.



Note: In the Experimental arm, Toca FC may begin up to 1 week earlier. In the SOC arm, Lomustine, Temozolomide or Bevacizumab may begin up to 2 weeks earlier.

7.8. Schedule of Events

Table 5: Schedule of Events (Experimental Arm) – Cycle Begins with Each Toca FC Dosing (6 Weeks Each)

Study Week	**W-3 (Screening)**	**W1D1 (Surgery)**	**W1[1] D7-21**	**W7**	**W8**	**W13**	**W19**		
Toca FC cycle/day				**C1D1[2]**	**C1D7**	**C2D1[2]**	**C3D1[2]**	**CXD1[2]**	**EOT[3]**
Informed consent	X								
History/Height	X								
Physical exam	X			X		X	X	X	X
Neurological examination (Neuro exam)	X			X		X	X	X	X
Vital signs	X			X		X	X	X	X
Weight	X			X		X	X	X	X
Karnofsky score	X			X		X	X	X	X
Complete blood count (CBC)	X			X		X	X	X	X
Chemistry panel	X			X		X	X	X	X
Urine analysis	X			X		X	X	X	X
Standard 12-lead electrocardiogram (ECG)				X[4]					
Human immunodeficiency virus (HIV)	X								
Pregnancy test[5]	X								
Tumor sampling[6]		X							
Cerebrospinal fluid (CSF)[7]		X							
Immune monitoring[8]	X	X[9]				X[10]	X[10]		X
Intracranial Toca 511		**X**							
Toca FC[11]				**X**[12]		**X**	**X**	**X**	
5-FC serum level[13]					X				
Antiviral antibodies	X					X[10]			X
Viral testing RNA (plasma)[14]			X	X[10]		X[10]		X[15]	X
Viral testing DNA (whole blood)			X	X[10]		X[10]		X[15]	X
Shedding			X[16]	X[16]		X[16]			X[16]
Adverse events[17]			X	X[10]	X	X[10]	X[10]	X[10]	X
Concomitant medications (Con meds) /Steroids	X		X	X	X	X	X	X	X

[1] Routine post-surgery visit
[2] Time points for assessments may vary by ±7 days for each visit date (Day 1 of each dosing cycle). If cycle either starts early or is delayed, assessment time points should shift accordingly.
[3] End of treatment (EOT) visit to be conducted within 30 days of confirmed progression or earlier, if due to a reason indicated in Section 8.3. Visit assessments are required.
[4] Obtain prior to Toca FC dosing and retrospectively collect electrocardiogram that is routinely obtained as part of standard of care prior to surgery
[5] All females are required to have a pregnancy test at screening
[6] Tumor samples to be obtained during initial study resection and if subject undergoes repeat craniotomy for tumor progression, see Section 11.13
[7] Collected at the time of surgery from the resection cavity, see Section 11.14
[8] Whole blood, plasma, and sampling for peripheral blood mononuclear cells (PBMCs), see Section 11.12
[9] Prior to Toca 511 administration
[10] Prior to Toca FC administration
[11] Approximately every 8 hours (Q8h) × 7 days with food, repeated every 6 weeks
[12] Beginning approximately 6 weeks post Toca 511 administration; may begin up to 1 week earlier and may be delayed if subject is unable to tolerate oral dosing
[13] Day 7 of Toca FC (or up to 3 days earlier; only during Cycle 1, unless dose changed or relevant toxicity occurs)
[14] If a subject who is asymptomatic is discovered on routine testing to have viremia > 125,000 copies/mL, viral testing will be repeated at least every two weeks until RNA results are BLOQ
[15] To be repeated every 24 weeks after Toca 511 administration beginning at C4D1 until EOT (ie, C8D1, C12D1, C16D1, etc). Refer to Table 11 for viral testing schedule during long-term follow-up. If viremia is suspected, ad hoc testing is required (see Section 11.15.3).
[16] Urine and saliva to be collected and will be tested ad hoc if viral DNA or RNA > BLOQ per protocol Section 11.15.1 and Section 11.15.2
[17] If a subject is admitted to the hospital with unexplained neurologic or constitutional symptoms but is not scheduled for protocol defined viral testing, Tocagen may request viral testing be performed per protocol Section 11.15.3.

Table 6: Schedule of Events (SOC Arm, Lomustine) – Cycle Begins with Each Lomustine Dosing (6 Weeks Each)

Study Week	**W-3 (Screening)**	**W1D1 (Surgery)**	**W1[1] D7-21**	**W7**	**W8**	**W13**	**W19**		
Lomustine cycle/day				**C1D1[2]**	**C1D7**	**C2D1[2]**	**C3D1[2]**	**CXD1[2]**	**EOT[3]**
Informed consent	X								
History/Height	X								
Physical exam	X			X		X	X	X	X
Neuro exam	X			X		X	X	X	X
Vital signs	X			X		X	X	X	X
Weight	X			X		X	X	X	X
Karnofsky score	X			X		X	X	X	X
CBC	X			X		X	X	X	X
Chemistry panel	X			X		X	X	X	X
Urine analysis	X			X		X	X	X	X
HIV	X								
Pregnancy test[4]	X								
Tumor sampling[5]		X							
CSF[6]		X							
Immune monitoring[7]	X	X				X[8]	X[8]		X
Lomustine[9]				**X[10]**		**X**	**X**	**X**	
Antiviral antibodies	X								
Adverse events			X	X[8]	X[11]	X[8]	X[8]	X[8]	X
Con meds/Steroids	X		X	X	X[11]	X	X	X	X
Select Investigator's choice of SOC			X						

[1] Routine post-surgery visit
[2] Time points for assessments may vary by ±7 days for each visit date (Day 1 of each dosing cycle). If cycle either starts early or is delayed, assessment time points should shift accordingly.
[3] End of treatment (EOT) visit to be conducted within 30 days of confirmed progression or earlier, if due to a reason indicated in Section 8.3. Visit assessments are required.
[4] All females are required to have a pregnancy test at screening
[5] Tumor samples to be obtained during initial study resection and if subject undergoes repeat craniotomy for tumor progression, see Section 11.13
[6] Collected at the time of surgery from the resection cavity, see Section 11.14
[7] Whole blood, plasma, and sampling for PBMCs, see Section 11.12
[8] Prior to lomustine administration
[9] Lomustine PO 110 mg/m2 every 6 weeks until EOT/PD
[10] May begin up to 2 weeks earlier if subject is recovered from surgery
[11] C1D7 AE and con med collection may be assessed by phone

Table 7: Schedule of Events (SOC Arm, Temozolomide) – Cycle Begins with Each Temozolomide Dosing (4 Weeks Each)

Study Week	**W-3 (Screening)**	**W1D1 (Surgery)**	**W1[1] D7-21**	**W7**	**W8**	**W11**	**W13**	**W15**	**W19**		
Temozolomide cycle/day				**C1D1[2]**	**C1D7**	**C2D1**	**C2D15[2]**	**C3D1**	**C4D1[2]**	**CXDX[2,3]**	**EOT[4]**
Informed consent	X										
History/Height	X										
Physical exam	X			X			X		X	X	X
Neuro exam	X			X			X		X	X	X
Vital signs	X			X			X		X	X	X
Weight	X			X			X		X	X	X
Karnofsky score	X			X			X		X	X	X
CBC	X			X			X		X	X	X
Chemistry panel	X			X			X		X	X	X
Urine analysis	X			X			X		X	X	X
HIV	X										
Pregnancy test[5]	X										
Tumor sampling[6]		X									
CSF[7]		X									
Immune monitoring[8]	X	X					X		X[9]		X
Temozolomide[10]				**X[11]**		**X**		**X**	**X**	**X**	
Antiviral antibodies	X										
Adverse events			X	X[9]	X[12]		X		X[9]	X[9]	X
Con meds/Steroids	X		X	X	X[12]		X		X	X	X
Select Investigator's choice of SOC			X								

[1] Routine post-surgery visit
[2] Time points for assessments may vary by ±7 days for each visit date (Day 1 or Day 15 of each alternating cycle). If cycle either starts early or is delayed, assessment time points should shift accordingly.
[3] Assessments occur every 6 weeks alternating between Day 1 and Day 15 (ie, C5D15, C7D1, C8D15, C10D1, C11D15, etc)
[4] End of treatment (EOT) visit to be conducted within 30 days of confirmed progression or earlier, if due to a reason indicated in Section 8.3. Visit assessments are required.
[5] All females are required to have a pregnancy test at screening
[6] Tumor samples to be obtained during initial study resection and if subject undergoes repeat craniotomy for tumor progression, see Section 11.13
[7] Collected at the time of surgery from the resection cavity, see Section 11.14
[8] Whole blood, plasma, and sampling for PBMCs, see Section 11.12
[9] Prior to temozolomide administration
[10] Initial dose 150 mg/m^2 or PO once daily for 5 consecutive days per 28 day treatment cycle, may be raised to 200 mg/m^2 once daily for 5 consecutive days in the following 28-day treatment cycles
[11] May begin up to 2 weeks earlier if subject is recovered from surgery
[12] C1D7 AE and con med collection may be assessed by phone

Table 8: Schedule of Events (SOC Arm, Metronomic Temozolomide) – Cycle Begins with Each First Daily Temozolomide Dosing (4 Weeks Each)

Study Week	**W-3 (Screening)**	**W1D1 (Surgery)**	**W1[1] D7-21**	**W7**	**W8**	**W13**	**W19**		
Temozolomide cycle/day				**C1D1[2]**	**C1D7**	**C2D15[2]**	**C4D1[2]**	**CXDX[2,3]**	**EOT[4]**
Informed consent	X								
History/Height	X								
Physical exam	X			X		X	X	X	X
Neuro exam	X			X		X	X	X	X
Vital signs	X			X		X	X	X	X
Weight	X			X		X	X	X	X
Karnofsky score	X			X		X	X	X	X
CBC	X			X		X	X	X	X
Chemistry panel	X			X		X	X	X	X
Urine analysis	X			X		X	X	X	X
HIV	X								
Pregnancy Test[5]	X								
Tumor Sampling[6]		X							
CSF[7]		X							
Immune monitoring[8]	X	X				X[9]	X[9]		X
Temozolomide[10]				X[11] →	→	→	→	→	
Antiviral antibodies	X								
Adverse Events	X		X	X[9]	X[12]	X	X[9]	X[9]	X
Con meds/Steroids	X		X	X	X[12]	X	X	X	X
Select Investigator's choice of SOC			X						

[1] Routine post-surgery visit
[2] Time points for assessments may vary by ±7 days for each visit date (Day 1 or Day 15 of each alternating cycle). If cycle either starts early or is delayed, assessment time points should shift accordingly.
[3] Assessments occur every 6 weeks alternating between Day 1 and Day 15 (ie, C5D15, C7D1, C8D15, C10D1, C11D15, etc)
[4] End of treatment (EOT) visit to be conducted within 30 days of confirmed progression or earlier, if due to a reason indicated in Section 8.3. Visit assessments are required.
[5] All females are required to have a pregnancy test at screening
[6] Tumor samples to be obtained during initial study resection and if subject undergoes repeat craniotomy for tumor progression, see Section 11.13
[7] Collected at the time of surgery from the resection cavity, see Section 11.14
[8] Whole blood, plasma, and sampling for PBMCs
[9] Prior to temozolomide administration
[10] Temozolomide PO 50 mg/m2 daily until EOT/PD
[11] May begin up to 2 weeks earlier if subject is recovered from surgery
[12] C1D7 AE and con med collection may be assessed by phone

Table 9: Schedule of Events (SOC Arm, Bevacizumab) – Cycle Begins with Bevacizumab Dosing (4 Weeks Each)

Study Week	**W-3 (Screening)**	**W1D1 (Surgery)**	**W1[1] D7-21**	**W7**	**W8**	**W9**	**W11**	**W13**		
Bevacizumab cycle/day				**C1D1[2]**	**C1D7**	**C1D15**	**C2D1**	**C2D15[2]**	**CXDX[2,3]**	**EOT[4]**
Informed consent	X									
History/Height	X									
Physical exam	X			X				X	X	X
Neuro exam	X			X				X	X	X
Vital signs	X			X				X	X	X
Weight	X			X				X	X	X
Karnofsky score	X			X				X	X	X
CBC	X			X				X	X	X
Chemistry panel	X			X				X	X	X
Urine analysis	X			X				X	X	X
HIV	X									
Pregnancy Test[5]	X									
Tumor Sampling[6]		X								
CSF[7]		X								
Immune monitoring[8]	X	X						X[9]	X[10]	X
Bevacizumab[11]				**X**[12]		**X**	**X**	**X**	**X**	
Antiviral antibodies	X									
Adverse Events			X	X[9]	X[13]			X[9]	X[9]	X
Con meds/Steroids	X		X	X	X[13]			X	X	X
Select Investigator's choice of SOC			X							

[1] Routine post-surgery visit
[2] Time points for assessments may vary by ±7 days for each visit date (Day 1 or Day 15 of each alternating cycle). If cycle either starts early or is delayed, assessment time points should shift accordingly.
[3] Assessments occur every 6 weeks alternating between Day 1 and Day 15 (ie, C4D1, C5D15, C7D1, C8D15, C10D1, etc)
[4] End of treatment (EOT) visit to be conducted within 30 days of confirmed progression or earlier, if due to a reason indicated in Section 8.3. Visit assessments are required.
[5] All females are required to have a pregnancy test at screening
[6] Tumor samples to be obtained during initial study resection and if subject undergoes repeat craniotomy for tumor progression, see Section 11.13
[7] Collected at the time of surgery from the resection cavity, see Section 11.14
[8] Whole blood, plasma, and sampling for PBMCs, see Section 11.12
[9] Prior to bevacizumab administration
[10] At W19 (C4D1), prior to bevacizumab administration
[11] Bevacizumab 10 mg/kg IV every 2 weeks
[12] May begin up to 2 weeks earlier if subject is recovered from surgery
[13] C1D7 AE and con med collection may be assessed by phone

Table 10: Assessments of Efficacy (All subjects)

Study Week	W-3 Screening	W1D3 Post-Surgery	W7 C1D1	W13	W19	W25	W31	W37	W43	W49	W55	WX	EOT	LTFU
Gd-MRI	X[1]	X[2]	X[3]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[5]	X[6]	X[7]
PRO questionnaire[8]	X		X	X	X	X	X	X	X	X	X		X	

[1] Gd-MRI within 21 days prior to randomization
[2] Gd-MRI within 48 h post resection
[3] Baseline Gd-MRI within 5 days before treatment with Toca FC or SOC
[4] Gd-MRI may vary by ± 7 days
[5] After the first year, Gd-MRI to be continued per standard of care (at least a minimum of every 12 weeks until EOT (Weeks 67, 79, 91, 103, 115, etc)
[6] Gd-MRI to be obtained for confirmation of progression, see Section 9.6 and Section 11.9; do not repeat if second imaging scan for progression already done
[7] Following EOT, MRI will be obtained per standard of care
[8] PRO questionnaires are repeated every 6 weeks, prior to Gd-MRI, until confirmed progression or for one year, whichever occurs first

Table 11: Toca 511 Long-term Follow-up after Progression (Experimental Arm)

Year post EOT/PD[1]	**0.5**	**1**	**1.5**	**2**	**2.5**	**3**	**3.5**	**4**	**4.5**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Physical	X	X	X	X	X	X	X	X	X	X										
Neuro exam	X	X	X	X	X	X	X	X	X	X										
Vital signs	X	X	X	X	X	X	X	X	X	X										
Weight	X	X	X	X	X	X	X	X	X	X										
Karnofsky score	X	X	X	X	X	X	X	X	X	X										
CBC	X	X	X	X	X	X	X	X	X	X										
Chemistry panel	X	X	X	X	X	X	X	X	X	X										
Viral Testing Blood[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Shedding[3]																				
Con meds	X	X	X	X	X	X	X	X	X	X										
Adverse Events[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Toca FC[5]																				
5-FC serum level[6]																				

[1] Time points for assessments may vary by ±14 days for each visit date
[2] Plasma (viral RNA) and whole blood (viral DNA) testing is to be repeated every 6 months through 5 years after Toca 511 administration; if positive at the last time point in year 5, then monthly testing will be repeated through year 15 until results are negative for two consecutive tests. If viremia is suspected, ad hoc testing is required (see Section 11.15.3).
[3] If viral testing positive, urine/saliva testing required with concurrent plasma (viral RNA) – monthly; if negative after 2 consecutive specimens, no testing required
[4] May be assessed by phone, letter or examination special attention to new malignancies
[5] Every 6 weeks if treatment continuing
[6] Day 7 (or up to 3 days earlier) if Toca FC dose is changed or related grade ≥ 3 toxicity

Table 12: Survival Follow-up (All subjects)

Year post EOT	**0.25**	**.5**	**.75**	**1**	**1.25**	**1.5**	**1.75**	**2**	**…**	**EOS[1]**
Survival[2]	X	X	X	X	X	X	X	X	X	X
Subsequent anti-cancer therapies	X	X	X	X	X	X	X	X	X	

[1] EOS is defined as death, withdrawal of consent for any contact including the collection and reporting of data, or lost-to-follow-up
[2] The site will contact the subject approximately every 3 months until EOS

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be eligible for study entry:

1. Subject has given written informed consent
2. Subject is between 18 years old and 75 years old, inclusive
3. Subjects must have histologically proven GBM or AA and:
   a. Must have received first-line multimodal therapy with surgery followed by temozolomide (unless known MGMT promoter unmethylated) and radiation (subjects with GBM must have received temozolomide and radiation concurrently)
   b. Must be in first or second recurrence (including this recurrence)
   c. Recurrence must be confirmed by diagnostic biopsy with local pathology review or contrast-enhanced MRI. If first recurrence of GBM is documented by MRI, an interval of at least 12 weeks after the end of prior radiation therapy is required unless there is either: i) histopathologic confirmation of recurrent tumor, or ii) new enhancement on MRI outside of the radiotherapy treatment field
4. Subjects must have measurable disease preoperatively, defined as at least 1 contrast-enhancing lesion, with 2 perpendicular measurements of at least 1 cm , as per RANO criteria
5. Subjects must be at least 4 weeks post last dose of temozolomide
6. Prior gamma knife, stereotactic radiosurgery, or other focal high-dose radiotherapy is allowed but the subject must have either histopathologic confirmation of recurrent tumor, or new enhancement on MRI outside of the radiotherapy treatment field
7. Based on the pre-operative evaluation by neurosurgeon, the subject is a candidate for $\geq$ 80% resection of enhancing region
8. IDH1 mutation status of the primary tumor must be available or tumor samples must be available for pre-randomization testing
9. Laboratory values adequate for patient to undergo surgery, including:
   a. Platelet count $\geq 60{,}000/mm^3$
   b. Hgb $\geq$ 10 g/dL
   c. Absolute neutrophil count (ANC) $\geq 1{,}500/mm^3$
   d. Absolute lymphocyte count (ALC) $\geq 500/mm^3$
   e. Adequate liver function, including:
      - Total bilirubin $\leq$ 1.5 x ULN (unless has Gilbert's syndrome)
      - ALT $\leq$ 2.5 x ULN

f. Estimated glomerular filtration rate of at least 50 mL/min by the Cockcroft Gault formula below:

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times [0.85 \; if \; Female]}{72 \times \text{Serum Creatinine (in mg/dL)}}$$

10. Women of childbearing potential (women who have not had ≥12 months of non-therapy-induced amenorrhea or are not surgically sterile) must have had a negative serum pregnancy test within the past 21 days and must use a birth control method in addition to barrier methods (condoms).
11. Subject or subject's partner is willing to use condoms for 12 months after receiving Toca 511 or until there is no evidence of the virus in the subject's blood, whichever is longer
12. The subject has a KPS ≥ 70
13. The subject is willing and able to abide by the protocol

8.2. Subject Exclusion Criteria

1. History of more than 2 prior recurrences (including this recurrence) of GBM or AA
2. History of other malignancy, unless the patient has been disease-free for at least 5 years. Adequately treated basal cell carcinoma or squamous cell skin cancer is acceptable regardless of time, as well as localized prostate carcinoma or cervical carcinoma in situ after curative treatment
3. Histologically confirmed oligodendroglioma or mixed glioma
4. Known 1p/19q co-deletion
5. A contrast-enhancing brain tumor that is any of the following:
   a. Multi-focal (defined as 2 separate areas of contrast enhancement measuring at least 1 cm in 2 planes that are not contiguous on either fluid-attenuated inversion recovery (FLAIR) or T2 sequences);
   b. Associated with either diffuse subependymal or leptomeningeal dissemination; or
   c. > 5 cm in any dimension
6. The subject has or had any active infection requiring systemic antibiotic, antifungal or antiviral therapy within the past 4 weeks
7. The subject has any bleeding diathesis, or must take anticoagulants, or antiplatelet agents, including nonsteroidal anti-inflammatory drugs (NSAIDs), at the time of the scheduled resection that cannot be stopped for surgery
8. The subject is HIV positive
9. The subject has a history of allergy or intolerance to flucytosine
10. The subject has a gastrointestinal disease that would prevent him or her from being able to swallow or absorb flucytosine

11. The subject received cytotoxic chemotherapy within the past 4 weeks (6 weeks for nitrosoureas) of the planned surgery date
12. The subject received any investigational treatment within the past 30 days or prior immunotherapy or antibody therapy within the past 45 days.
13. The subject is breast feeding
14. The subject intends to undergo treatment with the Gliadel® wafer at the time of this surgery or has received the Gliadel® wafer < 30 days from W1D1 (surgery)
15. The subject has received bevacizumab for their disease unless in the context of primary therapy for newly diagnosed glioma
16. For subjects planned to potentially receive bevacizumab, they have no evidence of uncontrolled hypertension (defined as a blood pressure of ≥ 150 mm Hg systolic and/or ≥ 100 mm Hg diastolic on medication) or active GI perforation
17. The subject has received systemic dexamethasone continuously at a dose > 8 mg/day for 8 weeks prior to the date of the screening assessment
18. Severe pulmonary, cardiac or other systemic disease, specifically:
    - New York Heart Association > Grade II congestive heart failure within 6 months prior to study entry, unless asymptomatic and well controlled with medication (see Appendix F)
    - Uncontrolled or significant cardiovascular disease, clinically significant ventricular arrhythmia (such as ventricular tachycardia, ventricular fibrillation, or Torsades des pointes), clinically significant pulmonary disease (such as ≥ Grade 2 dyspnea, according to CTCAE 4.03)
    - Subjects who have any other disease, either metabolic or psychological, which as per Investigator assessment may affect the subject's compliance or place the subject at higher risk of potential treatment complications

8.3. Subject Withdrawal Criteria

Any of the following will result in discontinuation from the treatment phase of the study (EOT):

1. Progression of disease (PD should be confirmed, see Section 11.9)
2. Withdrawal of consent for further treatment
3. The subject refuses to comply with the requirements for study evaluations/visits.
4. The subject experiences a severe adverse event that in the opinion of the PI or the Medical Monitor, is caused by, or exacerbated by, any of the study procedures or study drugs.
5. Investigator's or Sponsor's decision.
6. Decision to begin antiretroviral therapy.
7. Death

Subjects who discontinue treatment should complete the End of Treatment (EOT) procedures within 30 days of the decision to discontinue treatment phase or confirmed PD. Subjects who have received treatment with Toca 511 in this study will continue to be followed in accordance with regulatory requirements regarding monitoring of subjects in gene transfer trials for delayed adverse events (Section 11.16).

All withdrawn subjects will be followed for survival (Table 12) unless a specific request is made by the subject to discontinue the collection and reporting of data. Subjects will continue to be followed until EOS, defined as death, withdrawal of consent for the collection and reporting of data, or lost to follow-up. Public records may be used to collect survival data, ie, obituary notices and public database searches for survival information.

8.4. Replacement of Subjects

Replacement of subjects once randomized is not allowed.

9. TREATMENT OF SUBJECTS

9.1. Description of Study Drug

9.1.1. Experimental Arm

Table 13: Investigational Products Toca 511 and Toca FC

	Investigational Product	
Code Name:	Toca 511	Toca FC
Dosage Form:	Solution for injection	Tablet
Dose	4 mL	220 mg/kg/day
Route of Administration	Injection into the walls of the resection cavity (see Section 10.6.1)	Oral (see Section 10.6.2)
Physical Description	See Section 10.1	See Section 10.2

9.1.1.1. Administration of Toca 511

See Section 10.6.1.

9.1.1.2. Administration of Toca FC

9.1.1.2.1. Toca FC (Flucytosine) Dosing

The actual dose to be administered (approximately Q8h) should be calculated as follows:

- Multiplying the dose (220 mg/kg/day) by weight in kilogram to determine the total daily dose
- Dividing by 3 to determine the dose at each of 3 time points in a day
- Rounding up to the nearest 500 mg and dividing by 500 to obtain the number of tablets every 8 hours

Eg, 220 mg/kg x 68 kg = 14,960 mg divided by 3 = 4987 mg rounding up to 5000 mg/500 = 10 tablets every 8 hours

Calculate Toca FC dose at the start of each cycle using the weight at that cycle.

Note that regardless of body weight, a maximum of 18 Toca FC tablets may be administered every 8 hours (ie, total of 54 tablets for a total dose of 27,000 mg/day).

The Sponsor has developed an extended-release formulation of flucytosine, Toca FC, which can be dosed every 8 hours with food and does not contain lactose. This, coupled with a flatter time vs concentration curve, should result in improved compliance, improved blood level consistency through the day, and possibly improved tolerability. Subjects will be instructed to take the Toca FC tablets after a full meal in 3 equally divided doses administered as close to every 8 hours as possible. It is very important that Toca FC be taken after a full meal, as absorption is significantly reduced in the fasted state versus the fed state (refer to the Investigator's Brochure). Examples of such a meal may include but is not limited to eggs and bacon, fruit and toast, hot/cold cereals, soup and salad, pasta with meat or vegetables. For the bedtime dose, the meal could consist of a bowl of cereal, or a sandwich, cheese and several crackers, etc. The clinic staff should convey the subject's weight to the pharmacist for dispensing of Toca FC tablets.

9.1.1.2.2. Safety Criteria for Adjustment or Stopping Doses: Adjusting Dose of Toca FC Based on Observed Toxicity

Table 14: Safety Criteria for Adjustment or Stopping Doses of Toca FC

Toxicity Considered Related to Toca FC	**Dose Modification and/or Action**
Gastrointestinal toxicity (eg, nausea, vomiting, diarrhea)	• In the case of nausea or vomiting subject should be instructed to take the tablets over a 15 minute period of time and an anti-emetic should be prescribed if clinically indicated • In the case of diarrhea, an anti-diarrheal agent should be prescribed if clinically indicated • If gastrointestinal toxicity persists, Toca FC may be decreased from 7 to 5 days each cycle if an alternate cause for toxicity is not found
≥ Grade 3 non-hematologic toxicity (eg, elevated liver function test)	• Hold dosing of Toca FC until the abnormal values return to the levels specified in the Inclusion/Exclusion • The duration of Toca FC therapy may be decreased from 7 to 5 days each cycle if an alternate cause for toxicity is not found • Adjust concomitant medications which may be contributing (eg, anti-seizure drugs)
Acute cardiotoxic event or renal failure	• Initiation of dialysis should be considered
Alanine aminotransferase (ALT) ≥ 3 times upper limit of normal (ULN) and bilirubin ≥ 2 times ULN in absence of cholestasis or any other apparent cause	• Ensure that no other cause is found for the abnormality, including other drugs known to cause liver enzyme elevation • If no other cause is found, **permanently discontinue Toca FC** • Follow the subject with repeat chemistry testing every 2-3 days until recovery • Notify the Sponsor immediately by reporting the case as an SAE

Toxicity Considered Related to Toca FC	Dose Modification and/or Action
≥ Grade 3 hematologic toxicity (eg, anemia, leucopenia, thrombocytopenia)	• Hold dosing of Toca FC until the abnormal values return to the levels specified in the Inclusion/Exclusion criteria • The duration of Toca FC therapy should be decreased from 7 to 5 days each cycle ***or*** • If the Toca FC dose was increased previously, then reduce to the prior dose
Toca FC serum concentration > 200 µg/mL	• Reduce Toca FC to 170 mg/kg/day
Glomerular filtration rate (GFR) 26-50 mL/min	• Reduce Toca FC dose to 130 mg/kg/day
GFR < 26 mL/min	• Call Medical Monitor to discuss

9.1.1.2.3. Pharmacokinetic Criteria for Adjustment or Stopping Doses: Adjusting Dose of Toca FC Based on 5-FC Serum Concentration

The 5-FC serum concentration will be determined by drawing blood on Day 7 of dosing of Cycle 1 after steady state has been attained. Steady state is reached approximately after 3 days of dosing with Toca FC; thus, if needed, a time point between Days 4 and 7 is acceptable. The report of 5-FC serum concentration is provided by the central lab to the study site.

Dose reduction for Toca FC will be performed on the basis of tolerability (gastrointestinal and constitutional symptoms), renal blood test (including change in GFR), and hematologic and liver blood tests revealing toxicity; or, if Toca FC serum concentration is > 200 µg/mL.

A complete blood count (CBC) will be performed at the beginning of each cycle. Subjects who have Grade 3 or higher anemia, neutropenia or thrombocytopenia on this central testing, should have a local CBC performed prior to beginning their next cycle of Toca FC. Since Toca 511 is an integrating retrovirus, there is no maximum time after which Toca FC cannot be resumed.

Subjects with 5-FC serum concentrations less than or equal to 100 µg/mL and no tolerability or toxicity issues will have their Toca FC dose increased by 1 tablet every 8 hours (1,500 mg/day) starting at the subsequent cycle, however, the dose should not exceed 18 tablets per dose (54 tablets per day). Subjects with 5-FC serum concentrations greater than 100 µg/mL should not escalate the Toca FC dose.

For any dose adjustment, the 5-FC serum concentration testing should be tested during the cycle in which it was increased, after steady state has been attained (ie, Day 7, or between Days 3 and 7). Those subjects with relevant toxicity should also have the 5-FC serum concentration testing repeated. The Investigator may also request the 5-FC serum concentration during any cycle in which he/she is concerned about compliance, side effects, or significant changes in a subject's renal or hepatic function.

If the Toca FC dose is adjusted for any reason, the new dose must be clearly documented and conveyed to the investigational pharmacy.

9.1.1.2.4. Contraindications

Toca FC should not be given to a person with known flucytosine hypersensitivity.

9.1.1.2.5. Drug-drug Interactions

Drugs which impair glomerular filtration may prolong the biological half-life of flucytosine, and additional monitoring of kidney function should be considered if these drugs are required for any medical treatment of the subject.

9.1.1.3. Subject Stopping Rules

9.1.1.3.1. Late-occurring Adverse Events

Subjects may have to discontinue treatment for the following events:

- Persistent viremia (> 150,000 copies/mL by reverse transcriptase quantitative polymerase chain reaction [qRT-PCR] on 2 occasions separated by at least 1 month) with absence of clinical benefit such that the Investigator and the subject desire to institute antiretroviral therapy
- The occurrence of lymphoma or leukemia, the treatment of which would be interfered with by continued participation in the study
- Any unexplained deterioration of neurologic status

9.1.1.3.2. Institution of Anti-retroviral Therapy

In vitro and in vivo studies with Toca 511 confirm that its replication can be inhibited by AZT (zidovudine; Retrovir®) in concentrations that can be attained in plasma with oral dosing of 300 mg twice daily (BID). In addition, Viread® (tenofovir disoproxil fumarate, TDF) and Isentress® (raltegravir) have confirmed in vitro activity against Toca 511.

Subjects may be considered for anti-retroviral therapy based on the following criteria:

- Subjects with evidence of persistent viremia (> 150,000 copies/mL by qRT-PCR on 2 occasions separated by at least 1 month) should be considered for treatment with anti-retroviral medication.
- For subjects with evidence of persistent viremia (> 150,000 copies/mL by qRT-PCR on 2 occasions separated by at least 1 month) and clinical or radiographic evidence of tumor response, the decision regarding whether to use anti-retroviral therapy and when to use it, will be left to the discretion of the PI and the subject.

Please notify the Medical Monitor for any questions regarding antiretroviral therapy or if antiretroviral therapy is being considered. Note that no cases of persistent viremia have been seen in other trials of Toca 511 and Toca FC, and no subjects have required antiretroviral therapy to date.

9.1.2. Control Arm

Control arm subjects will be treated with one of the following standard of care options per Investigator's choice:

Table 15: Control Arm Products Bevacizumab, Lomustine, or Temozolomide

	Product		
Product Name:	Bevacizumab	Lomustine	Temozolomide
Dose	10 mg/kg	110 mg/m^2	50 mg/m^2 once daily continuously or Initial dose of 150 mg/m^2 once daily for 5 consecutive days per 28-day treatment cycle (may be raised to 200 mg/m^2 once daily for 5 consecutive days in the following 28-day treatment cycles)
Route of Administration	IV	PO	PO or IV

Treatment eligibility should be determined according to standard medical practice. The Investigator will select the SOC treatment during the routine post-op visit (approximately 7-21 days following surgery) taking into consideration the subject's clinical status following surgical resection of the tumor, and prior treatments. Necessary safety procedures and laboratory values in addition to the ones outlined in the protocol are to be captured according to institutional guidelines and manufacturer's instructions.

9.1.2.1. Administration of Bevacizumab

Beginning approximately 6 weeks (or as early as 4 weeks) after tumor resection, bevacizumab will be administered by IV infusion at 10 mg/kg and repeated every 2 weeks. Refer to the prescribing information and to institutional guidelines for details regarding the administration procedure.

9.1.2.2. Administration of Lomustine

Beginning approximately 6 weeks (or as early as 4 weeks) after tumor resection, lomustine will be administered as a single oral dose of 110 mg/m^2 and repeated every 6 weeks. Refer to the prescribing information and to institutional guidelines for details regarding the administration procedure.

9.1.2.3. Administration of Temozolomide

Beginning approximately 6 weeks (or as early as 4 weeks) after tumor resection, temozolomide will be administered per 1 of 2 options:

- at a dose of 50 mg/m^2 PO once daily continuously, or
- at an initial dose of 150 mg/m^2 IV or PO once daily for 5 consecutive days per 28-day treatment cycle that may be raised to 200 mg/ m^2 once daily for 5 consecutive days in the following 28-day treatment cycles

Refer to the prescribing information and to institutional guidelines for details regarding the administration procedure.

9.1.2.4. Dose Adjustments for Toxicities

Any toxicity associated or possibly associated with control arm treatment should be managed according to standard medical practice and regional prescribing information.

9.2. Concomitant Medications

Routine anesthetics and postoperative pain/nausea medications do not need to be recorded (first 24 to 48 hours following surgery). However, all other concomitant medications must be recorded from the time of consent until 30 days past the last dose of Toca FC or SOC. Subjects may use acetaminophen to manage mild pain or fever.

9.3. Prohibited Medications

Prior to EOT, the subject must not receive other medications or anti-cancer therapies to treat the disease under study. Immunosuppressive drugs, other than dexamethasone, should not be prescribed for the subject following administration of Toca 511. Subjects should be discouraged from using NSAIDs when Toca FC is being taken, as they may reduce the glomerular filtration rate. If an NSAID must be taken, use of a short acting agent, such as ibuprofen, is preferred.

Calcium containing antacids such as Rolaids® and Tums® can reduce the absorption of flucytosine and should not be taken during the time that the subject is taking Toca FC.

Surgicel®, Gelfoam, and Avitene should not be used for hemostasis during resection, as these agents may inactivate Toca 511. Following tumor resection and surgical team unblinding, any agent can be used in the control arm to maintain hemostasis. For local hemostasis that does not respond to conventional techniques during resection, Surgifoam sponge may be used in the experimental arm to control bleeding as it is biocompatible with Toca 511.

Investigational agents used to improve surgical resection (ie, 5-ALA fluorescence), craniotomy, wound healing, or recovery are allowed. Contact the Medical Monitor for information on other investigational agents used in surgery.

9.4. Treatment Compliance

Treatment compliance for oral therapies will be assessed by returned pill count during clinic visits in each cycle and recorded in the eCRF. Any discrepancies will be discussed with the subject prior to the subject leaving the clinic.

9.5. Randomization and Blinding

This is an open-label study. Following determination of subject eligibility, subjects will be randomized at the time of surgery in a 1:1 allocation to receive either Toca 511 and Toca FC or the Standard of Care treatment. The randomization will be stratified as follows:

- By geographical region (United States, Canada, Ex-North America)
- By IDH1 mutation status (present vs. absent)
- By KPS (70-80 vs. 90-100)

The subject will be considered randomized into the study once the assignment is received. The randomization number may not be reissued.

The intent of randomizing at the time of surgery is to reduce potential bias and maintain the subject blind until after surgery. Those subjects who will undergo surgery after hours should be randomized as close to the time of surgery as possible.

9.6. Treatment After EOT

Once a subject has met any of the criteria for withdrawal from the treatment phase of the study (EOT) as per Section 8.3, the subject will have a final visit for the treatment phase (designated as "EOT" in the SOE), after which any therapy that is chosen by the treating physician is allowed.

In the SOC arm, crossover to the Experimental arm is not allowed, unless the primary endpoints have been met and the Sponsor notifies the sites.

In the Experimental arm, the subject may continue on Toca FC after EOT as long as benefit is presumed, or switch to/add any therapy that is determined by the treating physician.

Subjects on both arms will stay on study for collection of survival data. The site will contact the subject by letter or phone on an every 3-month basis until EOS. The date of death needs to be captured and reported in the EDC (electronic data capture) system.

For subjects on both arms, follow-up cancer treatment will be reported in the EDC.

Due to the potential for pseudo-progression and to account for a possibly different imaging read-out by the independent reviewer, in both arms, if progression was determined locally by imaging, subjects should remain on treatment until a further imaging is performed and collected for independent review at least 1 month after the initial determination of progression, independent of the treatment.

For the SOE after EOT, please refer to Table 11 and Table 12.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Composition of Toca 511

Toca 511 (vocimagene amiretrorepvec) consists of a purified retroviral replicating vector encoding a modified yeast cytosine deaminase gene. Toca 511 is formulated as a sterile, buffered, pH neutral solution containing sucrose, mannitol, and human serum albumin, and is supplied in a Type I glass vial capped with a grey butyl stopper and sealed with an aluminum crimp top.

10.2. Composition of Toca FC

Toca FC is an extended-release formulation of flucytosine. Toca FC is supplied as 500 mg white, oblong tablets with "TOCA FC" debossed on one side and "500" on the other side.

10.3. Study Drug Packaging and Labeling

10.3.1. Packaging and Labeling of Toca 511

Toca 511 is supplied in a Type I glass vial capped with a grey butyl stopper and sealed with an aluminum crimp top. Each vial of the study drug will be labeled; please refer to the Pharmacy Manual for labeling details.

10.3.2. Packaging and Labeling of Toca FC

Toca FC will be supplied in labeled bulk drug bottles each containing 100 tablets. The pharmacist or Investigator will dispense the appropriate number of tablets for the 7-day dosing interval in plastic, child-proof containers. Please refer to the Pharmacy Manual for labeling details.

10.4. Study Drug Storage

10.4.1. Storage of Toca 511

Toca 511 is shipped on dry ice in insulated containers with a temperature probe to confirm shipping conditions. Toca 511 is to be stored in a secure freezer at -90°C to -65°C. The freezer must have a temperature recorder.

10.4.2. Storage of Toca FC

Toca FC tablets should be stored at controlled room temperature (25°C, 77°F); excursions are permitted to 15-30°C (59-86°F).

10.5. Study Drug Preparation

10.5.1. Preparation of Toca 511

Note: Because Toca 511 is a live virus, the vial cannot undergo terminal sterilization. The inside of the vial and its contents are sterile, but the outside of the vial is not sterile. Scrubbed

operating room (OR) personnel will need help from non-scrubbed OR personnel when removing the vector from the vial.

Study drug should be prepared on the day of surgery by thawing at ambient temperature for 30-60 minutes prior to use (or until completely thawed). Thawed Toca 511 is stable at room temperature for up to 10 hours. If the thawed product is not used within 10 hours, it should be discarded and should never be re-frozen.

10.5.2. Dispensing of Toca FC

The pharmacist or Investigator will dispense the appropriate number of tablets for each 7-day dosing interval. The calculation of dose is described in Section 9.1.1.2.1.

10.6. Study Drug Administration

10.6.1. Administration of Toca 511

Toca 511 is to be administered by intracranial injection into the wall of the subject's tumor resection cavity on Day 1. Approximately 40 injections of 100 µL will be administered, for a total delivery of 4 mL. For details of administration of Toca 511, please see Appendix C**.**

10.6.2. Administration of Toca FC

Approximately 6 weeks (may begin up to 1 week earlier) following intracranial injection of Toca 511), subjects will begin their first cycle of oral Toca FC (ie, 220 mg/kg/day for 7 days). The start of Toca FC therapy is considered to be Cycle 1 Day 1. The start of Toca FC may be delayed for medical causes. Cycles will be repeated approximately every 6 weeks and dosing will begin on Day 1 of each cycle.

Subjects will be instructed to take the Toca FC tablets after a meal in 3 equally divided doses administered as close to every 8 hours as possible.

It is very important that Toca FC be taken after a full meal, as absorption is significantly reduced in the fasted state versus the fed state (refer to the Investigator's Brochure).

Examples of such a meal may include but is not limited to eggs and bacon, fruit and toast, hot/cold cereals, soup and salad, pasta with meat or vegetables. For the bedtime dose, the meal could consist of a bowl of cereal, a sandwich, cheese and several crackers, etc.

It is not necessary for a subject to divide up the Toca FC dose unless the subject feels nauseous. If nausea occurs, the nausea may be reduced by having the subject spread the Toca FC tablets out over 15 minutes.

The calculated dose of Toca FC is to be taken approximately every 8 hours. Missed full doses of Toca FC should be made up if ≤ 4 hours have elapsed from the scheduled dose time; otherwise, subjects should wait until the next scheduled dose.

If the subject is unable to swallow the Toca FC, please contact the Medical Monitor to discuss options for continued treatment.

Toca FC may be taken until the Investigator decides that no further benefit can be derived from treatment or intolerance.

10.7. Study Drug Accountability

The Investigator and the investigational pharmacist must maintain accurate accounting of investigational product. During the study, the following information must be recorded:

- Date of receipt, quantity and identification, including lot number of the product received from the Sponsor
- Identification (ID) number and initials of the subject to whom the product is dispensed
- The date(s), quantity and lot number of the product dispensed
- Dates and quantity of product returned, lost or accidentally or deliberately destroyed

Accountability Records will be provided by the Sponsor unless provided by the site. They must be kept current and must be readily available for inspection.

The Investigator should not return clinical study materials to the Sponsor unless specifically instructed to do so by the Sponsor.

Any expired or unused vials or bottles of study drug should be retained. The Clinical Research Associate will routinely conduct an accountability of the expired and unused vials and authorize their destruction. If the participating pharmacy is prohibited by institutional policy from retaining expired/unused vials, the investigational pharmacist will then be responsible for documenting the destruction of the vials.

10.8. Toca 511 Handling and Disposal

Toca 511 is a live, replication competent retroviral vector. Precautions appropriate for a Risk Group 2 (RG-2) virus should be followed. Other examples of RG-2 viruses include the herpes simplex and hepatitis B viruses. Biosafety Level 2 (BSL-2) precautions should be followed when handling and disposing of Toca 511. These precautions have been summarized in Appendix A and can also be found in the Investigator's Brochure. Surgical and laboratory staff handling any blood, or fresh or frozen tumor specimens after Toca 511 delivery should be trained in biosafety precautions and should be made aware of potential risks from Toca 511 exposure prior to their involvement with this study.

Any unused Toca 511 drug product and any disposable instruments that have contacted the vector, such as syringes, biopsy needles, etc, should be carefully disposed of according to the institution's policies for disposal of biohazardous waste. Reusable instruments should be autoclaved. Any spills should be reported to the biosafety office and cleared as per the institution's procedures.

11. ON STUDY PROCEDURES AND EVALUATIONS

The following tests will be conducted according to the SOE (see Section 7.8). Documentation will be made in the subject's records for all examinations and assessments.

11.1. Informed Consent

Prior to the performance of any protocol specific procedures, written informed consent must be obtained by signing an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) approved Informed Consent Form (ICF). Results from physical exam, laboratory test, radiographic evaluations, or other routine medical care performed prior to the date of informed consent, but within the allowed timeframe for screening procedures, can be used for determining the subject's eligibility if obtained as part of the subject's standard of care. If such results or evaluations are used in the determination of eligibility, this must be clearly documented in the subject's source documents.

All materials (eg, radiographic images obtained for this study) used for the baseline assessments and follow-up of subjects, or for the investigation of adverse events, may be duplicated and made available to the Sponsor and/or an authorized independent body for review.

11.2. Screening Visit

The following procedures will be performed during the screening visit. The screening visit can be one visit, or several visits occurring over 21 days. All assessments must be completed within 21 days before randomization unless otherwise noted.

- Demography: including gender, date of birth, and race.
- Disease history:
  - A full history of the course of the subject's cancer, including date of first pathologic diagnosis
  - A copy of the subject's pathology report
  - Medical history: includes collection of the subject's demographic data and recording past and present illnesses
  - A baseline history of hypertension and antihypertensive medication use, from the time of informed consent, must be recorded for accurate assessment of hypertensive adverse events (AEs)
- Current medications: information about current medications will be collected from time of informed consent
- Physical examination including neurologic exam, height and weight
- Vital signs (temperature, blood pressure, pulse)
- Screening labs: complete blood count (CBC), chemistry panel (including electrolytes, blood urea nitrogen (BUN), creatinine with estimated glomerular filtration rate (GFR), total bilirubin, alkaline phosphatase, ALT and aspartate

aminotransferase (AST), lactate dehydrogenase (LDH), and uric acid), HIV, and pregnancy test (serum βHCG, for female subjects)

- Collection of plasma for antibody screening
- Collection of blood and plasma for immunologic monitoring testing (North American sites only)
- Urinalysis
- Karnofsky Performance Score
- Gadolinium-enhanced MRI scan (Gd-MRI)
- EQ-5D-5L, EORTC QLQ-C30, EORTC QLQ-BN20 questionnaires

Subjects who meet eligibility criteria will be randomized to either the Experimental arm (Toca 511 and Toca FC) or the control treatment arm.

11.3. Physical Examination

Physical examination in accordance with institutional practices should be completed by a physician or other health professional licensed to perform such examinations.

11.4. Neurologic Exam

The neurologic examination includes a mental status exam and evaluation of cranial nerve, motor, sensory, and cerebellar/gait function. Neurologic examinations should be completed by a physician or other health professional licensed to perform such examinations and if possible, the same individual should perform the neurologic exam throughout the study.

11.5. Vital Signs

Temperature, blood pressure, and pulse should be recorded at each visit. Weight will be recorded as indicated on the SOE. Please weigh the subject for dosing purposes according to the site's standard of care.

11.6. Karnofsky Performance Score

Karnofsky Performance Score will be recorded at baseline and at the subsequent intervals indicated in the SOE (Appendix E).

11.7. Dexamethasone Dose

The daily dose of dexamethasone is to be recorded for both arms in the eCRF. The Investigator may use whatever postoperative corticosteroid dosing regimen he/she is comfortable with.

11.8. Routine Laboratory Evaluations

CBC with differential and platelet count, chemistry panel (including electrolytes, BUN, creatinine, estimated GFR, total bilirubin, alkaline phosphatase, ALT and AST, LDH, and uric acid), and urinalysis (dip-stick or 24-hour protein determination) will be performed by a central laboratory as indicated on the SOE.

11.9. Neuroradiology

Gd-MRI scans will be performed at screening, post-surgery, baseline (defined as up to 5 days prior to initiation of Toca FC or SOC) and every 6 weeks thereafter (+/- 7 days) for the first year until confirmed progression, per Table 10. If Toca FC or SOC drug dosing cycles are delayed, Gd-MRI will maintain the every 6 week schedule.

For recurrent tumor, Gd-MRI scans will be evaluated using the Response Assessment in Neuro-Oncology Working Group (RANO) response criteria (Appendix D). Complete response (CR) and partial response (PR) must be confirmed by repeat scan performed at least 1 month later.

In order to account for the potential of pseudo-progression due to inflammation and immune-cell infiltration, progressive disease (PD) must be confirmed by repeat scan performed at least 1 month later, in all subjects, before discontinuing treatment.

As with all biologic/immunological therapies, it is possible that the tumor will not change size or will actually increase in size on early MRI scans before decreasing in size (pseudo-progression) (Huang 2015). Even for chemotherapy, Hess et al reported that of 375 subjects with recurrent gliomas studied in Phase 2 trials at MD Anderson and UCSF, the median time to response by MRI was 14 weeks with 74% of responses occurring by 26 weeks and 95% by 50 weeks (Hess 1999). Thus, it is imperative that investigators make every effort to have subjects complete this study.

Following confirmed progression, Gd-MRI may be performed according to the Institution's standard of care.

Scans will be evaluated by the clinical site as well as transmitted to an independent medical imaging organization for independent radiology review (IRR). Please refer to the imaging manual for instructions on obtaining and transferring images.

11.10. Standard 12-lead Electrocardiogram (Experimental Arm)

A standard 12-lead electrocardiogram will be obtained on Cycle 1 Day 1 prior to Toca FC dosing. The electrocardiogram that is routinely obtained as part of standard of care prior to surgery will be retrospectively collected.

11.11. Measurement of 5-FC Concentration (Experimental Arm)

During Cycle 1 of Toca FC dosing, the serum concentration will be measured once by drawing blood at Day 7 of Cycle 1 (or between Days 3 and 7). The Investigator may also determine the 5-FC serum concentration during any cycle in which he/she is concerned about compliance, side effects, or significant changes in a subject's renal or hepatic function. The Toca FC dose should be reduced if serum concentration is > 200 µg/mL, on the basis of tolerability (gastrointestinal and constitutional symptoms), renal blood test (including change in GFR), or hematologic and liver blood tests revealing toxicity, or increased if serum concentration is < 100 µg/mL (see also Section 9.1.1.2.2 and Section 9.1.1.2.3).

11.12. Immunologic Monitoring (North America Only)

Assays will be performed on samples from subjects in both arms to evaluate evidence for immunologic mechanisms of disease control. These may include tumor reactive PBMC measurement by stimulation via ex vivo glioma antigen presentation, flow cytometry based phenotyping of PBMCs with an effector, memory, Treg, and myeloid-derived suppressor cell panel. Blood may be used for genomic sequencing to help identify or interpret tumor genetic analysis. Blood samples will be collected using the kit and procedures supplied by the Sponsor, at the time points indicated in the SOE. Please refer to the Laboratory Manual for additional collection specifics.

Blood Collection (see SOE and Laboratory Manual

1. 50-100 mL whole blood collected in BD CPT™ tubes (provided) and processed by the clinical site within 2 hours of collection
2. 6 mL whole blood collected in K2-EDTA tubes (provided)

11.13. Processing of Tumor Samples

Frozen tumor samples and slides/blocks from the study surgical resection are required from all subjects. In addition, if the subject undergoes repeat craniotomy for recurrence or progression to remove all or part of his/her brain tumor, or if the subject develops a new malignancy, the Sponsor will request tissue samples to test for the presence of Toca 511.

11.13.1. Processing of Brain Tumor Slides/Blocks from Study Resection for Central Pathology

All subjects will have retrospective central pathology review from this surgical resection. At the time of tumor resection in both study arms, non-necrotic appearing tumor will be collected and processed for central pathological review. Slides or paraffin embedded blocks containing formalin-fixed tumor tissue representative of the recurrent high grade glioma diagnosis is the preferred sample.

Please refer to the Laboratory Manual for collection specifics.

11.13.2. Processing of Brain Tumor Samples from Study Resection for Sponsor

At the time of tumor resection in both study arms, non-necrotic appearing tumor from at least three spatially distinct sites (Site 1, Site 2, Site 3, etc) will be collected in addition to the sample collected for central pathology review. Each collection site sample will be evaluated by frozen section to determine tumor composition.

Please refer to the Laboratory Manual for collection specifics.

The Sponsor will supply the tubes for cryopreservation. The pathology report should specify the H&E interpretation and Ki67 that correlates with each numbered specimen.

11.13.3. Processing of Tumor Samples for Sponsor from Repeat Craniotomy

If the subject undergoes repeat craniotomy for recurrence or progression of his/her brain tumor, the Sponsor will request samples from the resected tumor in order to test for gene and protein

expression profiling, in an effort to correlate genotype with response to treatment. In addition, for subjects treated in the Experimental arm, the Sponsor will test for the presence of Toca 511 in the tumor.

Surgical and laboratory staff handling any blood, or fresh or frozen tumor specimens after Toca 511 delivery should be trained in handling and disposal techniques for a Risk Group 2 (RG-2) virus (specifically, BSL-2 practices) and should be made aware of potential risks from Toca 511 exposure. Refer to Appendix A for additional information.

11.13.4. Processing of Tumor Samples for Sponsor from Secondary Malignancy (Experimental Arm)

If a subject develops any new malignancy, the Sponsor will ask for sample(s) of this tumor in order to test for the presence of Toca 511.

11.14. CSF Collection at the Time of Surgery (North America Only)

An attempt will be made to assess circulating RNA expression signatures in cerebrospinal fluid (CSF). CSF collection at time of surgery from resection cavity is optional. Attempts should be made to minimize contamination by blood. Ad hoc CSF collection may be done in parallel with subsequent procedures that require draining of CSF, including placement of shunts (eg, occurrences of hydrocephalus). Lumbar punctures are not considered necessary for CSF collection, unless the Investigator deems appropriate and the subject consents.

Please refer to the Laboratory Manual for collection specifics.

11.15. Viral Testing

11.15.1. Viral Blood Testing

At the time points indicated in the SOE, whole blood will be tested for the presence of viral DNA by quantitative polymerase chain reaction (qPCR) and plasma will be tested for viral RNA by qRT-PCR.

Testing for antibodies to the Toca 511 virus will be performed at baseline in both the Experimental Arm and SOC arm. Subsequent time points will be performed as indicated on the SOE in the Experimental Arm.

11.15.2. Viral Shedding

Urine and saliva will be collected at the time points indicated in the SOE, but will be tested by qRT-PCR for the presence of viral RNA only if viral RNA in the plasma is greater than below the limit of quantitation (BLOQ).

11.15.3. Ad Hoc Viral Testing

If a subject is admitted to the hospital with unexplained neurologic or constitutional symptoms but is not scheduled for protocol defined viral testing, Tocagen may request viral testing be performed to include qPCR on whole blood, qRT-PCR on plasma, urine, saliva and cerebrospinal fluid (CSF) when available (eg, after placement of lumbar drain). If the plasma testing reveals viremia > 50,000 copies/mL of viral RNA, then testing will be repeated at least

every 2 weeks until RNA results are BLOQ. Any positive urine or saliva test will also be repeated at least every two weeks until results are BLOQ.

If a subject who is asymptomatic is discovered on routine testing to have viremia > 125,000 copies/mL, viral testing will be repeated at least every two weeks until RNA results are BLOQ. Any positive urine or saliva test will also be repeated at least every two weeks until results are BLOQ. Tocagen is responsible for requesting the ad hoc testing required.

11.15.4. Testing for Infected Cell Type and Possible Clonal Expansion

If whole blood qPCR is >1,500 copies/µg on a single occasion then a whole blood sample may be requested to determine infected blood cell types. Sites will be notified of the need for this testing by Tocagen.

If whole blood qPCR is >1,500 copies/µg on two consecutive tests at least one month apart, then LAM-PCR, or other assay that provides information on possible clonal expansion, will be performed and repeated if clinically indicated. Sites will be notified of the need for this testing by Tocagen.

11.15.5. Viral Testing During Long-term Follow-up

During the LTFU phase (see Table 11), plasma and whole blood will be tested for the presence of Toca 511 viral sequences by qRT-PCR (viral RNA) and qPCR (viral DNA), respectively, based on the following schedule:

Until the end of year 5:

a. If the subject is positive (has viral DNA or viral RNA > below limit of quantitation [BLOQ]) by qPCR or qRT-PCR, respectively, then testing will be conducted monthly. If the subject becomes negative (BLOQ) by qPCR and qRT-PCR, and is negative for two consecutive tests, then testing will be performed every 6 months thereafter.

b. If the subject is negative by qPCR and qRT-PCR, then testing will be performed every 6 months.

c. If the subject becomes positive by qPCR or qRT-PCR, then testing will revert to monthly. If the subject becomes negative by qPCR or qRT-PCR and is BLOQ for two consecutive tests, then testing will be performed every 6 months thereafter.

For years 6-15:

a. If the subject is positive by qPCR or qRT-PCR, then testing will be conducted monthly. If the subject becomes negative by qPCR or RT-PCR and is negative for two consecutive tests, then testing will be discontinued.

b. If the subject is negative by qPCR and qRT-PCR, then testing will be discontinued.

11.16. Monitoring for Delayed Adverse Events (Experimental Arm)

In accordance with regulatory requirements for gene transfer trials, for subjects treated in the Experimental arm, the following AEs should be recorded during the LTFU phase: any new solid tumor, hematologic malignancy, or myelodysplastic syndrome, any neurologic decline not

attributed to tumor progression and any Grade 3 or higher toxicity that is possibly, probably or definitely related to Toca 511 or Toca FC. Twice yearly clinic visits should be conducted with each subject to record potential delayed adverse events, until the end of year 5 following administration of Toca 511. During this part of the study, all subjects should be assessed for the occurrence of any new solid tumor, hematologic malignancy or myelodysplastic syndrome and any neurologic decline not attributed to tumor progression, and any Grade 3 or higher toxicity that is possibly, probably or definitely related to Toca 511 or Toca FC.

For the subsequent 10 years, subjects or caregivers should be given a wallet card similar to the example below to report delayed adverse events. Sites will be required to contact their subjects yearly (via telephone or mail) to facilitate with long term follow up and reporting of delayed adverse events in accordance with regulations. Subjects or caregivers should be specifically asked about the occurrence of any new solid tumor, hematologic malignancy or myelodysplastic syndrome, or disease progression leading to death. See Section 13 for additional details regarding the recording of AEs.

Study Tg 511-15-01 Patient ID Card
Patient name: _____ Pt. number:_____
Investigator's name: _____ Inv. Phone number: _____

I am a patient in a gene transfer-brain cancer study.
Regulatory authorities request 15 years of follow-up safety data. Please call the Investigator to report any health problems.

11.17. Patient Reported Outcome and Quality of Life Assessment

The tools to be used in this study are the EQ-5D-5L, the EORTC QLQ-C30, as well as the EORTC QLQ-BN20 in order to assess and quantify patient reported outcome and quality of life in this specific patient population. Instructions on usage will be provided separately. Information on hospitalizations that occur during the study will be collected as part of the QoL assessment.

11.18. Autopsy/Tissue Instructions (Experimental Arm)

Except in countries where request for autopsy is not allowed, all subjects participating in the experimental arm in this study will sign a consent form that indicates the Investigator or attending physician may ask the next of kin for permission to perform an autopsy in the event the subject expires. When such an autopsy is performed, the Sponsor will supply the pathologist with a map to guide the taking of specimens from the brain tumor. These specimens will need to be flash frozen. When possible, the Sponsor will send a representative to facilitate the sampling process. These specimens will be tested for the presence of vector and the presence of the CD gene. In addition, gene expression profiling may be performed to correlate genotype with drug activity. Biopsies from normal brain or other tissues may also be requested for viral testing.

12. ASSESSMENT OF EFFICACY

Efficacy assessments will include:

- Overall survival– time from randomization date to death due to any cause
- Durable response rate – the proportion of patients whose best response is either CR or PR lasting at least 24 weeks, according to modified RANO criteria (as per Appendix D) as assessed by independent radiology review (IRR), in addition to clinical status and steroid use
- Duration of durable response – time from documentation of durable response to disease progression or death due to disease progression
- Durable clinical benefit rate – the proportion of subjects whose best overall response is either CR or PR lasting at least 24 weeks, or stable disease (SD) lasting at least 18 months , according to modified RANO criteria as assessed by IRR, in addition to clinical status and steroid use
- Progression-free survival – time from randomization date to tumor progression based on modified RANO criteria as assessed by IRR, in addition to clinical status and steroid use, or death due to any cause
- Patient reported outcome – as assessed by the EQ-5D-5L, the EORTC QLQ-C30, and the EORTC QLQ-BN20

12.1. Analysis of Efficacy

Progression-free survival (PFS) will be determined based on the independent radiology review (IRR) using the baseline MRI which is the MRI scan just prior to initiating Toca FC dosing or systemic control treatment.

Progression is defined as ≥ 25% increase in size of enhancing tumor or any new tumor on MRI scans, or neurologically worse, and steroids stable or increased.

Overall survival will be analyzed using the randomization date as baseline.

In addition, landmark analyses of OS9, OS12, OS18, and OS24 will be performed.

Detailed analyses of efficacy are described in the statistical analysis plan (SAP).

13. ASSESSMENT OF SAFETY

For safety information on Toca 511 and Toca FC, please refer to the most recent version of the Investigator's Brochure. For safety information on lomustine, temozolomide, or bevacizumab, please refer to the current regional prescribing information.

13.1. Definitions

13.1.1. Definition: Adverse Event (AE) and Treatment-Emergent Adverse Event (TEAE)

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered casually related to the product. An AE can be any unfavorable and unintended sign, symptom, or disease temporarily associated with use of a drug, without judgment about causality. AEs include:

- Any deleterious change from the subject's baseline status, including an increase in the severity or frequency of a pre-existing abnormality or disorder;
- Concurrent illnesses;
- Injury or accidents;
- Subjective symptoms considered unfavorable by the reporter;
- Clinically significant physical examination, laboratory, imaging, or physiological testing abnormalities (abnormalities requiring treatment or a change in medication are AEs)
- Overdose

AEs do not include:

- Laboratory or test abnormalities that are not considered clinically significant
- Incidental findings on imaging that are not considered clinically significant
- Conditions for which a procedure was planned prior to signing the informed consent (eg, elective knee replacement)
- Conditions present at baseline which have not worsened
- Hospitalization solely to complete procedures, or for social reasons such as respite care
- Cosmetic procedures
- Pregnancy without complications [however, follow-up information will be requested on any pregnancy in either a subject or their partner]

In clinical studies, an AE can include an undesirable medical condition occurring at any time. In this study, any AE beginning from the time of surgery, for a minimum of 12 weeks, or to 30 days

after the last dose of Toca FC or SOC, whichever occurs last, whether or not it is related to the study, is considered "treatment-emergent" (TEAE), and must be recorded in the eCRF.

Reported AEs should be evaluated as medically appropriate and followed to resolution or until no further improvement is expected.

Cancer progression and cancer-related death are a study endpoint and will not be reported as an AE.

13.1.2. Definition: Serious Adverse Event

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
  NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was **at risk of death at the time of the event**; it does not refer to an event, which hypothetically might have caused death if it were more severe.
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

The onset date of an SAE is defined as the date on which the medical event began. Where the event represents worsening of an existing condition or prior event, the onset date should be the date the event became Grade 3. The end date is the date on which the event resolved or resolved with sequelae (where further improvement is expected to be minimal); this does not need to be the hospital discharge date.

13.1.3. Definition: Relationship to Investigational Product/Procedure

In this study, Toca 511, Toca FC, lomustine, temozolomide, and bevacizumab are considered investigational for safety analysis. The Investigator should indicate whether an AE is causally related to one of these investigational products. The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the AE should be classified as "unrelated." If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related."

The relationship of an adverse event to the investigational product should be classified by the Investigator using the following guidelines:

"Related" Categories

Definite: Experience follows a reasonable temporal association and could not have been explained by the subjects underlying condition, or recurs following with a re-challenge with the drug.

Probable: Experience follows a reasonable temporal association, is confirmed by improvement upon discontinuation of investigational product, and is not reasonably explained by the subject's clinical state.

Possible: Experience follows a reasonable temporal association, and is reasonably likely to have been caused by drug exposure, but may have been produced by the subject's clinical state or other factors.

"Unrelated" categories

Unlikely: Experience does not follow a clear temporal association, and is probably produced by the subject's clinical state or other factors.

Unrelated: No relationship between the experience and administration of the investigational product.

For this study, AEs that are considered by the Investigator to have a Possible, Probable, or Definite relationship to the investigational product are considered to be "related" to the investigational product; unlikely and unrelated are considered to be "not related" to the investigational product. Sponsor assessment of causality may differ from Investigator assessment in accordance with FDA guidance, Safety Reporting Requirements for INDs and BA/BE studies.

13.1.4. Definition: Severity of Adverse Events

The severity of an AE should be defined according to the National Cancer Institute (NCI) Common Toxicity Criteria Adverse Events (CTCAE) Version 4.03. AEs that are not described in the NCI CTCAE should be evaluated using the following guidelines:

1 = **Mild** AE: Awareness of symptom, but easily tolerated; usually transient requiring no special treatment; does not interfere with usual status or activities

2 = **Moderate** AE: May be ameliorated by simple therapeutic measures; may interfere with usual activities

3 = **Severe** AE: Incapacitating, inability to perform usual activities

4 = **Life threatening** consequences; urgent intervention indicated

5 = **Fatal** AE

It is important to distinguish between seriousness and severity of AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria listed in Section 13.1.2. An AE of severe intensity may not be considered serious.

13.2. Adverse Event Reporting Period

AEs and SAEs will be recorded from the time of surgery for a minimum of 12 weeks, or until 30 days after the last dose of Toca FC or SOC, whichever comes last. During the long-term follow-up period for delayed AE monitoring, any new solid tumor, hematologic malignancy or myelodysplastic syndrome, any neurologic decline not attributed to tumor progression, and any Grade 3 or higher toxicity that is possibly, probably, or definitely related to Toca 511 or Toca FC will be reported (see Section 11.16).

13.3. Recording Adverse Events

Adverse events will be recorded at the investigational site. However, abnormal values that constitute an SAE or lead to discontinuation of administration of study drug must be reported and recorded as an AE. Information about AEs will be collected from the time of surgery for a minimum of 12 weeks, or until 30 days after the last dose of Toca FC or SOC, whichever comes last. During the long-term follow-up period for delayed AE monitoring, any new solid tumor, hematologic malignancy or myelodysplastic syndrome, any neurologic decline not attributed to tumor progression, and any Grade 3 or higher toxicity that is possibly, probably or definitely related to Toca 511 or Toca FC will be reported. The AE term should be reported in standard medical terminology when possible. For each AE, the Investigator will evaluate and report the onset date, resolution date, intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the patient to discontinue treatment.

13.3.1. Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording AEs on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one AE term should be recorded in the event field on the Adverse Event eCRF.

13.3.2. Diagnosis versus Signs and Symptoms

For all AEs, a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (eg, record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by one AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

13.3.3. Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (eg, cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All AEs should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

13.3.4. Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on the Adverse Event eCRF. The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this.

A recurrent AE is one that resolves between patient evaluation time points and subsequently recurs. Each recurrence of an AE should be recorded separately on the Adverse Event eCRF.

13.3.5. Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an AE. A laboratory test result must be reported as an AE if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in more frequent unscheduled assessments or further diagnostic evaluation not mandated by protocol
- Results in a change in study treatment (eg, dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (eg, potassium supplementation for hypokalemia) or a change in concomitant therapy
- Clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (eg, alkaline phosphatase and bilirubin 5 times the ULN associated with cholestasis), only the diagnosis (ie, cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (eg, "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as hyperkalemia.

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

13.3.6. Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an AE. A vital sign result must be reported as an AE if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (eg, dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (including a diagnostic evaluation not mandated in this protocol) or a change in concomitant therapy
- Clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an AE.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (eg, high blood pressure), only the diagnosis (ie, hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

13.3.7. Abnormal Liver Function Tests

The finding of an elevated ALT or AST (> 3 × baseline value) in combination with either an elevated total bilirubin (> 2 × ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST > 3 × baseline value in combination with total bilirubin > 2 × ULN (of which 35% is direct bilirubin)

- Treatment-emergent ALT or AST > 3 × baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF and reported to the Sponsor immediately (ie, no more than one business day after learning of the event), either as an SAE or a non-serious AE.

13.3.8. Pre-existing Medical Conditions

A pre-existing medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A pre-existing medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (eg, "more frequent headaches").

13.3.9. Lack of Efficacy or Worsening of Disease

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as AEs. These data will be captured as efficacy assessment data only. In some cases, the expected pattern of progression will be based on RANO. In some cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression using objective criteria.

13.3.10. Hospitalization or Prolonged Hospitalization

Any AE that results in hospitalization (ie, in-patient admission to a hospital) or prolonged hospitalization should be documented and reported as an SAE except as outlined below:

The following hospitalization scenarios are not considered to be AEs:

- Hospitalization for respite care
- Planned hospitalization for a procedure or imaging required by the protocol, which cannot be completed as an outpatient procedure
- Hospitalization for a pre-existing condition, provided that all of the following criteria are met:
- The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease
- The patient has not suffered an AE
- Hospitalization due solely to progression of the underlying cancer

For any of the above, any associated AEs or complications should be reported as an SAE if they prolong hospitalization or otherwise meet the criteria for an SAE.

13.3.11. Patient-Reported Outcome Data

AE reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data.

13.4. Reporting Serious Adverse Events

All SAEs (related and unrelated) will be recorded from the time of surgery for a minimum of 12 weeks, or until 30 days after the last dose of Toca FC or SOC, whichever comes last. All SAEs must be reported to Tocagen Inc. within 24 hours of the first awareness of the event. The Investigator's causality assessment should be included at the time of reporting. As soon as possible, the Investigator must verify the accuracy of the information from the corresponding source documents. Tocagen will be notified of the SAE via email receipt of the completed SAE form (safety@tocagen.com). The Investigator may call the Medical Monitor listed in Table 1 to discuss the event, but all information must be reported on the SAE form.

Each SAE should be followed until resolution, or the Investigator determines the event has stabilized or reached a new baseline. All SAE follow up information should be reported to the Sponsor by updating the SAE form as soon as possible.

All safety queries must be answered and the query responses should be provided to Tocagen within the timeframe requested with the query. After the end of the study, any SAEs discovered by the Investigator and considered possibly or probably related to the investigational product, should be reported to safety@tocagen.com.

Tocagen is responsible for notifying the relevant regulatory authorities of certain events. It is the Investigator's responsibility to notify the IRB or IEC of all SAEs that occur at his or her site. Investigators will also be notified of all unexpected, serious, drug-related events (7- or 15-Day Safety Reports) that occur during the clinical trial. Each site is responsible for notifying its IRB or IEC of these additional SAEs.

13.5. Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that are attributed by the investigator solely to progression of disease or disease under study should be recorded only on the Death Report eCRF.

All adverse events resulting in death, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor. Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (eg, after autopsy), "unexplained death" should be replaced by the established cause of death.

13.6. Immediate Reporting Requirements from Investigator to Sponsor

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than one business day after the investigator learns of the event.

The following is a list of events that the investigator must report to the Sponsor within one business day after learning of the event, regardless of relationship to study drug:

- SAEs
- Pregnancies
- Any exposure or potential exposure to Toca 511 by a health care worker

The investigator must report new significant follow-up information for these events to the Sponsor within 24 hours after becoming aware of the information. New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

13.7. Reporting Requirements for Pregnancies

Female subjects of childbearing potential or male subjects will be instructed to immediately inform the investigator if they or their partner (in the case of a male subject) become pregnant during the study or within 12 months after administration of Toca 511 or 1 month after the last dose of Toca FC, whichever is later. Pregnancy should not be recorded on the Adverse Event eCRF but a pregnancy report worksheet should be completed and sent to safety@tocagen.com as soon as possible and no more than 24 hours after learning of the pregnancy.

Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the pregnancy should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (eg, an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported as soon as possible following the event.

13.7.1. Congenital Anomalies/Birth Defects and Abortions

Any congenital anomaly/birth defect in a child born to a female subject or partner of a male subject exposed to study drug should be classified as an SAE, recorded on an SAE form, and reported to the Sponsor within 24 hours after learning of the event. Any spontaneous abortion

should be reported in the same fashion (as the Sponsor considers spontaneous abortions to be medically significant events).

13.8. Follow-Up of Subjects after Adverse Events

13.8.1. Investigator Follow-Up

The investigator should follow each AE beginning from the time of surgery, for a minimum of 12 weeks, or to 30 days after the last dose of Toca FC or SOC, whichever occurs last. Events should be followed until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all SAEs considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of AEs (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

13.8.2. Sponsor Follow-Up

For SAEs, and pregnancies, the Sponsor or a designee may follow-up by query, telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (eg, from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

13.9. Post-Study Adverse Events

At EOT, the investigator should instruct each subject to report to the investigator any subsequent AEs that the subject's personal physician believes could be related to prior study drug treatment or study procedures.

The investigator should notify the Sponsor of any death, SAE, or other AE of concern occurring at any time after a subject has discontinued study participation if the event is believed to be related to prior study drug treatment or study procedures. The Sponsor should also be notified if the investigator becomes aware of the development of cancer or a congenital anomaly/birth defect in a subsequently conceived offspring of a female subject or partner of a male subject exposed to study drug.

For all patients randomized to the experimental arm please refer to Section 11.16 for instructions regarding additional monitoring for delayed adverse events.

13.10. Reporting Serious Adverse Events to the IRB/IEC

It is the Investigator's responsibility to report SAEs to the IRB or IEC according to the requirements of the IRB/IEC.

13.11. Independent Data Monitoring Committee (IDMC)

An IDMC will be chartered and composed of medical/clinical experts and one statistician. The IDMC is an autonomous group that will periodically review study results to assure subject safety in this study as well as review the planned interim analyses data. Prior to initiation of this study,

a formal IDMC charter will be reviewed and agreed by both the Sponsor and IDMC. In addition, the process and detailed steps will be specified in the charter.

The IDMC members will not be involved in the operations of the study, nor will they have any conflict of interest concerning the outcome of the study. The members of the IDMC will be required to disclose, in writing, any financial interest in Tocagen.

To discharge its duties efficiently, the IDMC will evaluate the data related to safety and determine if the assumptions underlying the design of the study remain valid during the study. Based on safety data and monitoring procedures, the IDMC will make independent recommendations on continuing, stopping, or modifying the study. The IDMC will report its recommendations to the Sponsor. The Sponsor will have the option of acting on the recommendations of the IDMC with regards to trial modifications. The IDMC will monitor all deaths, SAEs, withdrawals, and any other event it considers relevant to the overall responsibility as defined in the charter. A designated independent statistician will periodically provide safety reports to the IDMC. In addition, the IDMC may request collection of additional data or updating of data if necessary to interpret the data under review.

The IDMC may hold additional meetings as necessary. Written conclusions of the IDMC meetings will be issued to authorized Sponsor representatives. Any significant findings or recommendations by the IDMC will be promptly communicated to all Investigators by the Sponsor. IDMC procedures, format of reports, and stopping rules, will be prospectively detailed in the IDMC charter.

14. STATISTICS

14.1. General Considerations

This is a multicenter, randomized, open-label study of Toca 511 and Toca FC versus SOC, that comprises Investigator's choice of single agent chemotherapy (lomustine or temozolomide) or bevacizumab administered to subjects undergoing resection for first or second recurrence (including this recurrence) of GBM or AA. The primary objective is to compare the overall survival (OS) of the subjects between the two arms.

Statistical analysis will be done by the Sponsor or under the authority of the Sponsor. A general description of the statistical methods to be used in the analysis of efficacy and safety is outlined below. Detailed analyses are described in the SAP.

14.1.1. Multiplicity Adjustments

For the primary endpoint of OS, 2 interim analyses and 1 final analysis are planned for this study after observing approximately 50% (129 events) and 75% (193 events) of the total required number of events (257 events), respectively. The OS endpoint will incorporate group sequential design with the O'Brien-Fleming boundaries as implemented by Lan-DeMets alpha spending method. This method ensures that the type I error rate is not inflated. The exact significance levels will be determined according to the observed number of events at the time of analysis. At the time of the first interim analysis of OS, it is anticipated that all 380 subjects would have been enrolled into the study.

For the secondary endpoints of DRR, DCBR, DDR, and OS12, the Holm's procedure will be used to adjust for multiplicity at an overall significance level of 0.05 (two-sided).

14.1.2. Validation

All analyses will be performed using SAS V9.4 (SAS Institute, Inc., Cary, North Carolina) or higher. Validation and quality control of the tables, listings, and figures containing the results of the statistical analysis of the data will follow appropriate SOPs from the designated vendor.

14.2. Determination of Sample Size

Subjects will be randomized in a 1:1 ratio to receive Toca 511 and Toca FC or SOC. Subjects will be stratified according to (1) geographical region (United States vs Canada vs Ex-North America), (2) IDH1 mutation status (present vs absent), and (3) KPS (70-80 vs 90-100).

An overall type I error rate of 5% is planned for this study.

The assumed median OS for subjects in the control arm is 9.8 months (Reardon 2017), and the median OS for subjects in the Toca 511 and Toca FC arm is 14.3 months (based on preliminary Phase 1 data). With an assumed active enrollment duration of 28 months and an additional 18 months of follow-up, a sample size of approximately 380 subjects in total is planned to achieve the required number of 257 death events to detect a hazard ratio (HR) of 0.685 at a two-sided alpha of 0.05 and a power of 85%. The sample size was calculated using East® 6.4.

14.3. Handling of Dropouts and Missing Data

Every effort will be made to determine each subject's progression and survival information. However, subjects may drop out of the study at any time and withdraw their consent to collect follow-up information.

14.4. Analysis Population(s)

All efficacy analyses and subject disposition will include the intent-to-treat population (ITT) and efficacy evaluable population. The ITT population includes all randomized subjects classified according to their assigned treatment group irrespective of the actual treatment received.

The safety population will include all subjects who received at least surgery. For safety populations, treatment assignment will be based on the treatment actually received.

Efficacy Evaluable Population: All randomized subjects who have received surgery and at least one dose of Toca FC or one dose of SOC prior to EOT. The subjects will be classified according to their assigned treatment group irrespective of the actual treatment received.

14.5. Subject Disposition

Subject disposition information will be summarized for all subjects by arm. Summaries will include: the number of randomized subjects, the number of subjects in each analysis population, the number of subjects completing the study, and the primary reason for discontinuation.

14.6. Demographic and Baseline Characteristics

Demographic and baseline variables include: age, sex, ethnicity, and race. Other baseline characteristics include: relevant medical history, KPS, and neuro-oncology history. Demographic and baseline characteristics will be summarized for ITT Populations by arm.

14.7. Concomitant Medications

Verbatim terms on case report forms will be mapped to Anatomical/Therapeutic/Chemical (ATC) class and Generic Drug Names using the World Health Organization Drug Dictionary (WHO-DD). Concomitant medications are those medications taken after the initial dose of study drug.

Concomitant medications will be summarized by arm.

14.8. Efficacy Analyses

All continuous variables will be summarized using number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum. Binary variables will be summarized with n and percent. The Kaplan-Meier product limit method and Cox proportional hazards model will be used to estimate the time-to-event variables and to obtain the HR along with the associated confidence intervals. The 6 months, 9 months and other landmark time survival rates will be estimated using the Kaplan-Meier method. Unless otherwise specified, stratified log-rank test will be used to test the treatment effect for time-to-event variables, while the Cochran-Mantel-Haenszel (CMH) test will be used to test the binary variables. For time-to-event variables, a subject without an event at the time of analysis will be censored at the last known date the

subject did not have a documented event. Subgroup analysis will be performed base on the stratification variables as well as other pre-specified subgroups prescribed in the SAP.

The secondary endpoints are durable response rate, durable clinical benefit rate, duration of durable response, and overall survival at 12 months.

14.9. Safety Analyses

14.9.1. Adverse Events

All adverse event summaries by arm will be restricted to treatment-emergent adverse events (TEAE), which are defined as those AEs that occurred after surgery; and those existing AEs that worsened during the study, for a minimum of 12 weeks, or until 30 days after the last dose of Toca FC or SOC, whichever came last. If it cannot be determined whether the AE is treatment emergent due to a partial onset date, then it will be counted as such. Verbatim terms on case report forms will be mapped to preferred terms and system organ classes using the MedDRA dictionary.

14.9.2. Clinical Laboratory Evaluation

Laboratory parameters will be summarized using descriptive statistics at screening (baseline) and at each post-baseline time point by arm. Changes from baseline will also be summarized. In addition, change from pre-systemic treatment (prior to first dose of Toca FC or chemotherapy or bevacizumab) will also be summarized.

Shift tables will be provided to assess changes in laboratory values from screening (baseline) and change from pre-systemic treatment (prior to first dose of Toca FC or chemotherapy or bevacizumab) to follow-up. In addition, shift tables will be provided using “worst grade” from screening or pre-systemic treatment.

14.9.3. Karnofsky Performance Status

KPS will be summarized using descriptive statistics at screening (baseline) and at each post-baseline time point by arm. Mean changes from baseline will also be summarized. In addition, change from pre-systemic treatment (prior to first dose Toca FC or chemotherapy or bevacizumab) will also be summarized.

14.9.4. Vital Signs

Summary tables of vital signs will be generated. Vital signs will also be provided in a listing by subject.

14.9.5. Physical Examination

Summary tables of physical examination will be generated. Physical examination will also be provided in a listing by subject.

14.9.6. Neurological Examination

Using a 5-point Likert Scale (5 = Definitely better, 4 = Possibly better, 3 = Unchanged, 2 = Possibly worse, 1 = Definitely worse), mean overall neurological status as reported by the

Investigator compared to the W7 C1D1 visit at each subsequent assessment will be summarized by arm. In addition, a shift table will be generated by domain (Mental Status, Cranial Nerves, Motor, Sensory, and Cerebellar/Gait) from pre-systemic treatment to subsequent visits. The shift can be from normal to abnormal or vice-versa and presented by arm.

14.9.7. Current Steroid Dose

Total daily steroid dose (dexamethasone in mg/day) will be summarized using descriptive statistics at screening (baseline) and at each post-baseline time point by arm. Mean changes from baseline will also be summarized. In addition, change from pre-systemic treatment (prior to first dose of Toca FC or chemotherapy or bevacizumab) will be summarized.

14.9.8. Other Safety Labs

For summary of viral testing results from the Toca 511 and Toca FC arm only, there will be two categories of subjects: (1) BLOQ or (2) with quantitative values, in qPCR or qRT-PCR. Viral DNA and RNA as determined by qPCR (copies/μg) and qRT-PCR (copies/mL), respectively, will be summarized using descriptive statistics by visit and, in addition, peak qPCR and peak qRT-PCR will be included in the same table.

Antibody change from screening (baseline) over time will also be included in a listing for subjects in the Toca 511 and Toca FC arm only.

14.9.9. Patient Reported Outcome/Quality of Life

Patient reported outcome will be assessed using the EORTC Quality of Life Questionnaires Core 30 and Brain 20 (EORTC-QLQ30/EORTC QLQ-BN20), as well as the EQ-5D-5L.

In order to quantify health economy aspects, number and durations of hospitalizations will be collected.

Please refer to the description of these assessments in the SAP.

15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

15.1. Study Monitoring

Before an investigational site can enter a subject into the study, a representative of Tocagen Inc. will evaluate the site to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Tocagen Inc. or its representatives. This will be documented in a Clinical Study Agreement between Tocagen Inc. and the Investigator.

During the study, a monitor from Tocagen or its representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the electronic case report forms (eCRFs) with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (eg, clinic charts).
- Record and report any protocol deviations not previously sent to Tocagen
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to Tocagen and those SAEs that met criteria for reporting have been forwarded to the IRB/EC

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

15.2. Inspections

Authorized representatives of Tocagen, a Regulatory Authority, an Independent Ethics Committee or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP) guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements. The Investigator should contact Tocagen immediately (within 24 hours) if contacted by a Regulatory Agency about an inspection.

15.3. Institutional Review Board (IRB)/ Ethic Committee (EC)

The Principal Investigator (PI) must obtain IRB/EC approval for the investigation. Initial IRB/EC approval, and all materials approved by the IRB/EC for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

15.4. Curriculum Vitae and Medical Licenses

The PI is responsible for ensuring that the study is being conducted by qualified personnel. Documentation of these qualifications must be maintained within the Regulatory Binder, and includes the following:

Curriculum Vitae (CV): CVs for the PI and all Sub-investigators listed on the Form FDA 1572 must be signed and dated. These CVs must show affiliation with the institution conducting the study and be current within two years of the personnel initiating their participation in the study.

Medical Licenses: Medical licenses (physicians, physician assistants, nurses) listed on the Form FDA 1572 must be kept current, and copies must be maintained in the Regulatory binder during the entire period of the person's participation in the study.

15.5. Financial Disclosure

Documentation of each Investigator's proprietary or financial interest in Tocagen Inc. is required by the US Code of Federal Regulations (21 CFR 54). A financial disclosure form provided by the Sponsor must be completed, signed, and dated by the PI and each Sub-investigator listed on the Form FDA 1572. This form must be executed prior to the personnel's participation in the study. Each Investigator must inform the Sponsor of any change in his/her financial interest in the Sponsor for up to 1 year after the end of the study.

The US Securities and Exchange Commission (SEC) prohibits any person who has material, non-public information concerning Tocagen or a possible transaction involving Tocagen from purchasing or selling securities in reliance upon such information or from communicating such information to any other person or entity under circumstances in which it is reasonably foreseeable that such person or entity is likely to purchase or sell such securities in reliance upon such information.

16. INSTITUTIONAL BIOSAFETY COMMITTEE (IBC)

For US clinical sites, the site at which this trial is being conducted will ensure that an Institutional Biosafety Committee (IBC) is in place that is composed of at least 5 appropriately-qualified members. The IBC will ensure that the site conforms to the requirements set forth in the Section IV-B-2 of the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules, promulgated by the NIH/Office of Biotechnology Activities (NIH/OBA). The Investigator will be responsible for petitioning the IBC and obtaining approval prior to enrolling any subject in the study. The Investigator will also be required to obtain and follow all biohazard safety guidelines promulgated by the IBC, and to report all findings as required to the IBC and to Tocagen for reporting to NIH/OBA.

This protocol and any accompanying material provided to the subject (such as subject information sheets, Informed Consent Form, or descriptions of the study used to obtain informed consent) will be submitted by Tocagen to the legally constituted and chartered Institutional Biosafety Committee (IBC). Additional materials, such as the Investigator's Brochure, will be submitted to the IBC according to the specific Committee and federal (United States' National Institutes of Health or foreign equivalent) requirements. Each site will be approved by the IBC in accordance with local procedures and country specific regulatory requirements. Documentation of IBC approval must be in place prior to product shipment to the site. At the discretion of the specific IBC and within federal requirements, IBC oversight of individual sites may be terminated provided (1) all subjects at that site have completed dosing by at least 90 days, and (2) all investigational materials have been fully accounted for and either returned to Tocagen, destroyed on site, or shipped to a duly licensed destruction facility and a shipping and inventory reconciliation records have been filed.

17. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, Tocagen or its representative will monitor for compliance closely and may conduct a quality assurance audit.

18. ETHICS

18.1. Ethics Review

The final study protocol, including the final version of the Informed Consent Form/Patient Information Sheet, subject recruitment procedures (eg, advertisements), information about payments and compensation available to subjects, and any amendments must be approved by a properly constituted IRB or IEC in compliance with current regulations of the US FDA, ICH guidelines, and any Country specific regulations. Specifically, the study must not be initiated until the Investigator has provided Tocagen with documentation of IRB/IEC approval of the protocol, the Informed Consent Document, and all recruiting materials. In addition, prior to their implementation or use, there must be documented IRB/IEC approval for the following: protocol amendments, revised Informed Consent Documents, subject recruitment materials (eg, advertisements), and study related supplements that are provided to study subjects.

The PI must make timely and accurate reports to the IRB/IEC on the progress of the study, at intervals not exceeding one year, as well as satisfying any other local IRB/IEC regulations regarding reporting, including reporting on safety aspects of the study (eg, SAEs, safety letters). The study must receive documented IRB/IEC approval annually. Furthermore, at the completion or early termination of the study, a final report must be made to the IRB/IEC by the Investigator within the applicable IRB/IEC timeframes.

It is the Investigator's obligation to maintain an IRB/IEC correspondence file and to make this available for review by Tocagen representatives as part of the study monitoring process. Copies of all correspondence between the Investigator and the IRB/IEC (including all attachments to any correspondence) must be provided for the Tocagen internal file.

18.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH and local Good Clinical Practice, applicable regulatory requirements and the Tocagen's policy on Bioethics.

18.3. Written Informed Consent

The Investigator(s) at each center will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated informed consent must be obtained before conducting any study-specific procedures.

The Investigator(s) must maintain the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the patient.

18.4. Subject Confidentiality

The Investigator must ensure that the subject's confidentiality is maintained. Subject medical information obtained for the purposes of this study is confidential, and disclosure to third parties, other than those noted below, is prohibited. Subjects should not be identified by name, social security number or medical record number on any documents or materials (samples, slides) sent to Tocagen or its representatives (eg, data management organization) or during verbal communications. Subjects should be identified only by their initials and protocol-assigned subject ID number.

For clinical sites in the US, study personnel should follow the requirements of the Health Insurance Portability and Accountability Act (HIPAA).

All clinical information is confidential, but data generated for this study must be available for inspection on request to representatives of the US FDA, other national or local regulatory or health authorities, Tocagen representatives, and the associated IRB/IEC.

All records must be kept in a secured area.

19. DATA HANDLING AND RECORDKEEPING

19.1. Data/Document

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of study treatment are complete, accurate, filed, and retained. Examples of source documents include hospital records, clinic and office charts, laboratory notes, memoranda, subject's diaries or evaluation checklists, dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiche, X-ray film and reports, records kept at the pharmacy and the laboratories.

19.2. Data Management

Data will be collected via electronic CRF (eCRFs). This data will be electronically verified through use of programmed edit checks. Any discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes to the data.

19.3. Inspection of Records

Tocagen and its representatives will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and any other records relative to study conduct.

19.4. Retention of Records

Investigators are required to maintain all study documentation, including documents created or modified in electronic format, for at least 25 years following the completion of the study. ICFs and adequate records for the receipt and disposition of all study medications must be retained for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated, or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA and other applicable Regulatory Authorities are notified, unless a longer period is required by applicable law or regulation.

19.5. Compensation, Insurance and Indemnity

Information regarding compensation, insurance, and indemnity will be provided to the Investigator in the Clinical Trial Agreement.

19.6. Publication Policy

All information obtained as a result of this study should be regarded as confidential.

Information regarding use or publication of study related information will be provided to the Investigator in the Clinical Trial Agreement.

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21. APPENDICES

APPENDIX A. BIOSAFETY LEVEL II SUMMARY INFORMATION

Precautions appropriate to a Risk Group 2 virus are recommended for the ampho-MLV in Toca 511 (US NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules). There are 4 risk groups, with Risk Group 1 posing the least danger and Risk Group 4 being the most dangerous to work with. RG-2 viruses are defined as those agents that are associated with human disease which is rarely serious and for which preventive or therapeutic interventions are often available. For comparison purposes, herpes simplex virus and hepatitis B virus are also classified as Risk Group 2 viruses. Dealing with Risk Group 2 viruses requires certain precautions referred to as Biosafety Level 2 (BSL-2) practices. These practices are summarized below. Further information can be obtained from the local site Institutional Biosafety Committee.

1. Standard Microbiological Practices (BSL-2)
    a. Access to the clinical areas with the study agent is limited or restricted by the Principal Investigator when work with organisms containing recombinant or synthetic nucleic acid molecules is in progress.
    b. Work surfaces are decontaminated at least once a day and after any spill of viable material.
    c. All contaminated liquid or solid wastes are decontaminated before disposal.
    d. Mechanical pipetting devices are used; mouth pipetting is prohibited.
    e. Eating, drinking, smoking, and applying cosmetics are not permitted in the work area. Food may be stored in cabinets or refrigerators designated and used for this purpose only.
    f. Persons wash their hands: (i) after handling materials involving organisms containing recombinant or synthetic nucleic acid molecules and animals, and (ii) when exiting the clinical areas with the study agent.
    g. All procedures are performed carefully to minimize the creation of aerosols.
    h. Clinical trials of lesser biohazard potential can be conducted concurrently in carefully demarcated areas of clinical areas with the study agent.
2. Special Practices (BSL-2)
    a. Contaminated materials that are to be decontaminated at a site away from the clinical areas with the study agent are placed in a durable leak-proof container which is closed before being removed from the clinical areas with the study agent.
    b. The Principal Investigator limits access to the clinical areas with the study agent. The Principal Investigator has the final responsibility for assessing each circumstance and determining who may enter or work in the clinical areas with the study agent.
    c. The Principal Investigator establishes policies and procedures whereby only persons who have been advised of the potential hazard and meet any specific entry requirements (eg, immunization) may enter clinical areas with the study agent.

d. When the organisms containing recombinant or synthetic nucleic acid molecules in use in the clinical areas with the study agent require special provisions for entry (eg, vaccination), a hazard warning sign incorporating the universal biosafety symbol is posted on the access door to the clinical areas with the study agent work area. The hazard warning sign identifies the agent, lists the name and telephone number of the Principal Investigator or other responsible person(s), and indicates the special requirement(s) for entering the clinical areas with the study agent.

e. An insect and rodent control program is in effect.

f. Laboratory coats, gowns, smocks, or uniforms are worn while in the clinical areas with the study agent. Before exiting the clinical areas with the study agent for non-study agent areas (eg, cafeteria, library, administrative offices), this protective clothing is removed and left in the clinical areas with the study agent or covered with a clean coat not used in the clinical areas with the study agent.

g. Animals not involved in the work being performed are not permitted in the clinical areas with the study agent.

h. Special care is taken to avoid skin contamination with organisms containing recombinant or synthetic nucleic acid molecules; gloves should be worn when handling study agent and when skin contact with the agent is unavoidable.

i. All wastes from clinical areas with the study agent are appropriately decontaminated before disposal.

j. Hypodermic needles and syringes are used only for parenteral injection and aspiration of fluids. Only needle-locking syringes or disposable syringe-needle units (ie, needle is integral to the syringe) are used for the injection or aspiration of fluids containing organisms that contain recombinant or synthetic nucleic acid molecules. Extreme caution should be used when handling needles and syringes to avoid autoinoculation and the generation of aerosols during use and disposal. Needles should not be bent, sheared, replaced in the needle sheath or guard, or removed from the syringe following use. The needle and syringe should be promptly placed in a puncture-resistant container and decontaminated, preferably autoclaved, before discard or reuse.

k. Spills and accidents which result in overt exposures to organisms containing recombinant or synthetic nucleic acid molecules are immediately reported to the Institutional Biosafety Committee and NIH/OBA. Reports to NIH/OBA shall be sent to the Office of Biotechnology Activities, National Institutes of Health, 6705 Rockledge Drive, Suite 750, MSC 7985, Bethesda, MD 20892-7985 (20817 for non-USPS mail), 301-496-9838, 301-496-9839 (fax). Medical evaluation, surveillance, and treatment are provided as appropriate and written records are maintained.

l. When appropriate, considering the agent(s) handled, baseline serum samples for clinical and other at-risk personnel are collected and stored. Additional serum specimens may be collected periodically depending on the agents handled or the function of the facility.

m. A biosafety manual or standard operating procedures are prepared or adopted. Personnel are advised of special hazards and are required to read and follow instructions on practices and procedures.

3. Containment Equipment (BSL-2)

   a. Biological safety cabinets (Class I or II) other appropriate personal protective or physical containment devices are used whenever:

      i. Procedures with a high potential for creating aerosols are conducted. These may include centrifuging, grinding, blending, vigorous shaking or mixing, sonic disruption, opening containers of materials whose internal pressures may be different from ambient pressures.

      ii. High concentrations or large volumes of organisms containing recombinant or synthetic nucleic acid molecules are used. Such materials may be centrifuged in the open clinical areas with the study agent if sealed beads or centrifuge safety cups are used and if they are opened only in a biological safety cabinet.

4. Facilities of Clinical Areas with the Study Agent (BSL-2)

   a. The clinical areas with the study agent are designed so that they can be easily cleaned

   b. Bench tops are impervious to water and resistant to acids, alkalis, organic solvents, and moderate heat

   c. The furniture of the clinical areas with the study agent is sturdy and spaces between benches, cabinets, and equipment are accessible for cleaning

   d. Each clinical area with the study agent contains a sink for hand washing

   e. If the clinical areas with the study agent have windows that open, they are fitted with fly screens

   f. An autoclave for decontaminating clinical areas with the study agent waste is available

5. Toca 511 Specific Practices

   a. Specific BSL-2 training must be completed by all personnel who will be handling the virus. Such training must be documented in writing and updated at appropriate intervals.

   b. Protective gowns, gloves and splash guards or goggles must be worn when handling the virus.

   c. Hospital labs and venipuncturists already practice standard precautions equivalent to BSL-2, so that drawing blood from study participants should not require any change in their procedures.

   d. All contaminated surgical tools should either be disposed of with the biohazardous waste or submitted for sterilization as per operating room standard operating procedures.

e. For spills outside of a biological safety cabinet the following procedures may be used:
   i. Wearing gloves, splash guard and gown, cover the spill with paper towels and then pour freshly prepared disinfectant (usually 1:9 dilution of bleach) on paper towels.
   ii. Leave disinfectant in contact with spill for at least 20 minutes.
   iii. Pick up paper towels and discard into biohazard waste container.
   iv. Any broken glass should be picked up with forceps and placed in sharps container.
   v. Wipe the spill area with disinfectant and then remove and dispose of gloves properly and wash hands with soap or suitable alternative.
   vi. Notify the local Institutional Biosafety Committee of all spills/accidents for potential review.

f. All procedures associated with a high risk of aerosolization, such as centrifugation or sonication, should be performed in a biosafety cabinet.

g. Any personnel who experience a splash or spray accident involving a mucous membrane, or who experience a puncture or needle stick injury that is potentially contaminated with virus, should immediately notify the Principal Investigator.
   i. Please see Investigator's Brochure Appendix 1 for additional details

APPENDIX B. INDEPENDENT BIOSAFETY RISK ASSESSMENT OF TOCA 511

To assist in site Institutional Biosafety Committee understanding of the biological risks, Tocagen commissioned an independent, third-party risk assessment of Toca 511 for biosafety considerations. The findings are summarized below.

1. Pathogenicity: Amphotropic MLV (also called Moloney murine leukemia virus or MMLV) infects human cells, but is not known to cause human disease (ie, is not a human pathogen). No known case of human disease attributed to MLV has ever been reported. Previously, a report regarding the report of possible association between Toca 511 and lymphoma in mice, additional information presents a plausible argument that because the proposed mechanism of lymphomagenesis has only been documented in mice to date, and relies on the presence of endogenous mouse retroviruses, the risk of Toca 511 causing lymphoma in humans is likely to be extremely low.
2. Spill/splash/aerosol/needlestick hazards: All of these are potential routes of accidental exposure. The needleless vial access reduces the likelihood of spill or splash. The use of a blunt needle for intra-operative injection reduces the risk of needlestick. Surgeons will be familiar with techniques for drawing up liquids from unsterile vials for intra-operative injection in a sterile field, and using direct visualization in a spatially familiar tumor cavity should further reduce the risk of accidental self-injection. The Institutional Biosafety Committee should assess training for appropriate individuals prior to their involvement with this study. Personnel working with the vector directly should wear protective gowns, gloves, masks, and eye protection. In the event of accidental infection, AZT may be used because it inhibits Toca 511 replication in vitro and in vivo at standard therapeutic levels. In response to RAC concerns about a single-drug anti-retroviral regimen, Tocagen confirmed in vitro activity against Toca 511 with the anti-retroviral drugs (zidovudine; Retrovir®), Viread® (tenofovir disoproxil fumarate, TDF), and Isentress® (raltegravir). A Safety Data Sheet (SDS) is available.
3. Horizontal transmission: In mice, the most permissive species, there has been no evidence of horizontal transmission of vector in mouse co-habitation studies. However, the RAC noted the detection of vector DNA (provirus) and RNA in the blood suggests that replication competent virus may circulate in the blood for several weeks, and this raises the prospect of transmission to close contacts, such as through sexual contact. The RAC asked that the risk of sexual transmission and the need for contraception should be emphasized in the consent form. Study subjects will be monitored for the presence of viral DNA or RNA at multiple time-points throughout the study, as well as periodic monitoring of urine and saliva to determine if any viral DNA or RNA is present.
4. Vertical transmission: Vertical transmission is the main route of dissemination of MLV in mice. Pregnancy testing is done once, within 21 days before Toca 511 dosing. Females are to use effective contraception in addition to condoms while participating in the study. Males and females are to use condoms for 12 months. Toca 511 was not detected in semen in dog studies; no human data are provided. It is unknown if the virus is present in semen or vaginal secretions, male and female patients receiving Toca 511

should be advised to use condoms or condoms and spermicide for at least twelve months following receipt of Toca 511.

5. Genome integration: In mice, oncogenesis can occur when newborn or immunosuppressed animals are infected. The current human clinical study contains inclusion and exclusion criteria designed to exclude severely immune suppressed subjects from entering the study. Amphotropic MLV integrates into the human cell genome as part of its replication cycle. Therefore, human insertional mutagenesis is possible, as was seen in the X-SCID protocols in which immune precursor cells transduced with a nonreplicating RV vector. In those experiments, the transduced cell line was intended to expand, whereas in this study the CD 'suicide gene' is expected to result in the death of transduced cells upon administration of 5-FC. The cases of lymphoma seen in mice are described as related to recombination events of the amphotropic *env* gene with endogenous mouse polytropic and ecotropic *env* gene sequences, a mechanism that would be specific to mice and not affect humans who lack significant homologous sequences allowing such homologous recombination. Finally, the immediate risk of recurrent high grade glioma arguably trumps the theoretical late (2-5 year) risk of a secondary malignancy; lymphoma offers more treatment options.
6. Immune response (to vector and to transgene product): The virus inside the tumor does not induce a host immune response significant enough to truncate the transduction process. In prior studies, Tocagen notes that in research subjects injected with Toca 511, almost all had some low level of pre-existing anti MLV antibodies, as has been previously observed (Martineau 1997), and when viremia occurred, it cleared following the appearance of increased levels of anti-Toca 511 antibodies, within 1-2 months after administration of Toca 511. Also, outside of the tumor, the virus is controlled by an intact immune system.
7. Adventitious infection: Human serum albumin present in the formulation confers a theoretical risk of containing undetected infectious agents. Although not strictly in this category, another risk is recombination events between the RRV and other retroviruses, such as HIV or endogenous human retroviruses. Patients are required to test negative for HIV at enrollment. Published experiments suggest that retrovirus genomes are prone to recombination in general but no specific recombinants with human sequences (including Human Endogenous RetroVirus [HERV] sequences) have been observed, and MLV does not detectably package HERV sequences. Even if recombinants were to occur, it is not clear they would be harmful to the human host; a cell infected with a recombinant virus carrying the CD suicide gene would presumably be vulnerable to 5-FC killing.
8. Environmental implications: MLV infection usually clears from mice following acute viremia. With other ampho-MLVs, infection in non-human primates has resulted in long-term control or clearance. The natural mode of spread by in utero vertical transmission, and the use of the product in this medically controlled setting do not seem to pose risk to the environment.

APPENDIX C. INTRACRANIAL VECTOR DELIVERY PROCEDURE (HAND/SYRINGE METHOD)

Materials Required

- Appropriate number of vials of Toca 511 thawed (exterior of vial is not sterile)
- Epimed blunt nerve block needle - supplied by Sponsor
- Sterile syringe without needle
- Appropriately sized needleless vial adapter(s) depending on the vial size - supplied by Sponsor
- Safety goggles

Procedure

1. The surgeon and other scrubbed personnel should wear safety goggles or splash guard.
2. Carefully remove the cap and swab the rubber stopper of each vial of Toca 511 with alcohol for 10 seconds and air dry prior to placing a needless vial adaptor on a vial.
3. Vial to Syringe Transfer:
   a. Surgeon to draw approximately 0.5 mL of air into each syringe.
   b. Assistant to hold vial extended to allow surgeon to connect without compromising surgeon sterility.
   c. Surgeon and assistant to connect syringe to vial adapter without compromising surgeon sterility.
   d. Inject air from the syringe into the vial. This will make it easier to pull maximum volume from the vial without cavitation.
   e. Using the needleless vial adapter and syringe, draw up volume of vector for each syringe (multiple syringes can be used for the approximately 4 mL total dose). Remember that the outside of the vial is not sterile and multiple vials may be needed obtain the full 4 mL dose.
   f. Pull the entire contents from the vial into the syringe and repeat these steps for all other vials to prepare the 4 mL dose.
   g. Remove any air bubbles from all filled syringes prior to disconnecting the syringe from the needless adaptor and connecting the Epimed needle.
   h. Attach Epimed nerve block needle to syringe and carefully prime the needle by watching for the first drop of vector to appear at the needle opening (priming will only need to be performed prior to the first use of each prepared syringe and Epimed needle). Gauze or other absorbent material should be used to absorb any droplets that are expressed.

4. Ensure that the resection cavity is dry and that hemostasis has been obtained prior to beginning injections of vector.

Intracranial Injections

1. As much as possible, injections will be made perpendicular to the cavity wall at a depth of 1 cm with initial injections starting at the lowest point of the cavity working towards the highest point of the cavity, as fluid will collect and obscure lower injection site surfaces.
2. Intracranial injections will be made into the walls of the resection cavity. The intraventricular or subarachnoid space will be avoided. Inject the entire contents of the syringes as follows: approximately 40 injections of approximately 100 µL will be made, for a total of 4 mL. Each injection should be made slowly over ~10 seconds and the needle left in place for 20-25 seconds before removing. Slowly remove the needle and repeat the injection taking care to distribute the injections over the entire resection cavity.
3. Dispose of the syringe and Epimed needle in biohazard container.
4. EVERY EFFORT SHOULD BE MADE **NOT** TO IRRIGATE OR SUCTION THE RESECTION CAVITY ONCE THE INJECTIONS HAVE BEGUN.

Cleanup

1. Deposit all used vials of vector, syringe, and any other contaminated disposables in the appropriate biohazard container.
2. Change gloves before closing.
3. Call a member of the biohazard department to remove the biohazard container from the OR.
4. Complete OR worksheet and transmit to study coordinator.

APPENDIX D. MODIFIED RESPONSE ASSESSMENT IN NEURO-ONCOLOGY (RANO) CRITERIA

Response	Criteria (Wen 2010)
Complete Response (CR)	• Disappearance of all enhancing measureable and non-measurable disease sustained for a minimum of 1 month • Stable or improved FLAIR/T2 lesions • No new lesions • Clinical status is stable or improved • Not receiving corticosteroids (physiologic replacement doses are acceptable) The RANO criteria have been modified as follows: • Subjects with enhancing non-target disease will be allowed to achieve a complete response if there is evidence for complete resolution of enhancement. • Subjects with only non-enhancing non-target disease will be allowed to achieve a complete response if there is evidence for complete resolution. These modifications are being made to allow for subjects who responded with and without measureable disease identified at baseline to be evaluated, as this study is being conducted in the resection setting. The introduction of drugs that affect vascular permeability was an important reason for the development of the RANO criteria, which specify that an assessment of complete response cannot be made for subjects who do not have measurable disease identified on the baseline scan. Given that they have undergone resection, it is likely that many subjects in this study will not have measurable disease on their baseline MRI. The proposed modifications of the RANO criteria are based on RECIST criteria, which have allowed for an assessment of complete response with the disappearance of target and non-target lesions.
Partial Response (PR)	• ≥ 50% reduction in size (tumor's largest cross-sectional area) of enhancing measureablelesions sustained for a minimum of 1 month o ≥50% decrease compared with baseline in the sum of products of perpendicular diameters (SPD) of all measurable enhancing lesions • No progression of nonmeasurable disease • No new lesions • Stable or improved FLAIR/T2 lesions • Clinical status is stable or improved • Corticosteroid dosage at the time of scan should not be greater than the dosage at the time of baseline scan

Progression (PD)	• ≥ 25% increase in size of enhancing all measurable lesions compared with smallest tumor measurement obtained either at baseline or best response following initiation of therapy, while on a stable or increasing dose of corticosteroids. o ≥25% increase in sum of the products of perpendicular diameters (SPD) • Significant increase in FLAIR/T2 lesions compared with baseline or best response following initiation of therapy, not caused by comorbid events (eg, radiation therapy, ischemic injury, seizures, postoperative changes, or other treatment effects), while on a stable or increasing dose of corticosteroids • Presence of new lesions • Clinical deterioration not attributable to other causes apart from the tumor or decreases in corticosteroid dose • Death or deteriorating condition • Clear progression of nonmeasurable disease
Stable Disease (SD)	• Stable FLAIR/T2 lesions on corticosteroid dose no greater than baseline • Clinical status is stable

APPENDIX E. KARNOFSKY PERFORMANCE STATUS

Description	Score
Able to carry on normal activity and to work; no special care needed.	100 Normal no complaints; no evidence of disease. 90 Able to carry on normal activity; minor signs or symptoms of disease. 80 Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70 Cares for self; unable to carry on normal activity or do active work. 60 Requires occasional assistance, but is able to care for most of his personal needs. 50 Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40 Disabled; requires special care and assistance. 30 Severely disabled; hospital admission is indicated although death not imminent. 20 Very sick; hospital admission necessary; active supportive treatment necessary. 10 Moribund: fatal processes progressing rapidly

Reference: http://www.npcrc.org/usr_doc/adhoc/functionalstatus/Karnofsky%20Performance%20Scale.pdf

APPENDIX F. NEW YORK HEART ASSOCIATION CLASSIFICATION

Table 16: NYHA Classification

Class	Definition
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea, or anginal pain
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea, or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity results in fatigue, palpitation, dyspnoea, or anginal pain.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Reference: The Criteria Committee for the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels Ninth Edition. Little Brown and Company. 1994: 253-255.

APPENDIX G. CHANGES IN THE CONDUCT OF THE STUDY

The original protocol submitted to the IND was Version 1 dated 09 April 2015. Following FDA and Recombinant DNA Advisory Committee (RAC) review, the protocol was revised (Version 3 dated 02 July 2015) and submitted to the IND and clinical sites, which was the first version under which patients were enrolled.

The following is a list of major changes made to the protocol since the study was initiated. Additional minor changes throughout the body of the protocol have been made for document consistency and for clarification of procedures.

Amendment	Change
Protocol Version 4 dated 23 Sep 2016	• Revised secondary objectives to align with statistical analysis plan • Increased the frequency of survival follow-up (every 3 months) and clarification to follow-up instruction for subjects receiving Toca 511 (to be followed until death or 15 years, whichever occurs first) • Revised withdrawal criteria to indicate that the progression of disease (PD) should be confirmed prior to discontinuation • Provided clarification text to dosing instruction to indicate that a **maximum** of 18 Toca FC tablets may be administered every 8 hours (ie, total of 54 tablets for a total dose of 27,000 mg/day), regardless of body weight • Provided instruction to dose modification for Toca FC serum concentration > 200 µg/mL • Provided dose modification and/or action for gastrointestinal toxicity, hematologic toxicity ≥ Grade 3, any acute cardiotoxic event or renal failure, or a GFR of 26-50 mL/min or < 26 mL/min • Revised dose adjustment to indicate that dose reduction of Toca FC will be performed on the basis of tolerability • Provided clarification text to indicate that Toca FC should be made up if ≤ 4 hours have elapsed from the scheduled dose time • Removed pump method for vector delivery procedure, only hand/syringe method will be used • Provided guidance for modified RANO criteria to allow for subjects who responded with and without measurable disease identified at baseline to be included in the evaluation

Amendment	Change
Protocol Version 5 dated 18 Sep 2017	• Modified the study to a seamless design by removing the enrollment pause between Phase 2 and Phase 3 portions of the study • Increased subject enrollment from approximately 370 to 380 subjects and extended the completion date of the studied period • Revised the primary objective of the study to include assessment of overall survival and durable response rate • Revised secondary objectives to include assessments and evaluations for durable clinical benefit rate, duration of durable response, and to provide clarity to other secondary assessments • Updated criteria for evaluation and statistical methods to address changes to the study objectives • Removed requirement of subject diaries for documentation of treatment compliance and study drug accountability
Protocol Version 6 dated 18 Oct 2017	• Revised the primary objective of the study to remove the assessment of durable response rate • Revised secondary objectives to include assessments and evaluations for durable response rate • Updated criteria for evaluation and statistical methods to address changes to the study objectives

Electronic Signature Page For Tg 511-15-01 (TOCA 5) - Protocol

Reason for signing: Approved	Name: Asha Das Role: CDMA Date of signature: 19-Oct-2017 00:47:00 GMT+0000

STATISTICAL ANALYSIS PLAN

Version: 5

Date of Plan:

12 November 2018

Based on:

Protocol Number: Tg 511-15-01

A Phase 2/3 Randomized, Open-Label Study of Toca 511, a Retroviral Replicating Vector, Combined With Toca FC versus Standard of Care in Subjects Undergoing Planned Resection for Recurrent Glioblastoma or Anaplastic Astrocytoma

Protocol Version: 6

Protocol Date: 18 Oct 2017

Study Drug:

Toca 511 and Toca FC

Sponsor:

Tocagen Inc.
4242 Campus Point Court, Suite 500
San Diego, CA 92121
(858) 412-8400

This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

STATEMENT OF CONFIDENTIALITY

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LIST OF ABBREVIATIONS

Abbreviation	Term
AA	anaplastic astrocytoma
AE	adverse event
ATC	Anatomic Therapeutic Chemical
BLOQ	below the limit of quantitation
C1D1	Cycle 1 Day 1
CBC	complete blood count
CMH	Cochran-Mantel-Haenszel
CR	complete response
CRF	case report form
CSR	clinical study report
CTCAE	Common Toxicity Criteria Adverse Events
DCBR	durable clinical benefit rate
DDR	duration of durable response
DNA	deoxyribonucleic acid
DOB	date of birth
DRR	durable response rate
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of Treatment (at the time of confirmed progression or discontinuation of study treatment)
EQ-5D-5L	EuroQol - 5 Dimensions - 5 Levels
GBM	glioblastoma multiforme
HR	hazard ratio
HRQoL	Health-Related Quality of Life
ICH	International Conference on Harmonization
IDH1	isocitrate dehydrogenase 1
IRR	independent radiology review
ITT	Intent-to-Treat
IV	intravenous
KPS	Karnofsky Performance Status
MedDRA	Medical Dictionary for Regulatory Activities Terminology

Abbreviation	Term
MGMT	O6-methylguanine-DNA methyltransferase
MMRM	Mixed Effects Model for Repeated Measurements
MRI	magnetic resonance imaging
NCI	National Cancer Institute
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PFS	progression-free survival
PO	oral (administration)
PR	partial response
PRO	Patient Reported Outcome
QoL	Quality of Life
qPCR	quantitative polymerase chain reaction
qRT-PCR	quantitative reverse transcriptase polymerase chain reaction
RANO	Response Assessment in Neuro-Oncology Working Group
RNA	ribonucleic acid
s.d.	standard deviation
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis System
SD	stable disease
SOC	standard of care
SOE	Schedule of Events
TEAE	treatment-emergent adverse event
Toca 511	RRV containing modified yeast cytosine deaminase transgene
Toca FC	5-fluorocytosine, 5-FC, flucytosine extended-release tablets
TTD	time to deterioration
TU	transducing units
VAS	Visual Analog Scale
WBC	white blood cell
WHO	World Health Organization

REVISION HISTORY

The following is a summary of changes made to the statistical analysis plan (SAP) since the study was initiated.

Version	Change
Version 2 dated 22 Feb 2017	Revisions based on the amended protocol (Version 4): • Revised secondary objectives to include assessments of objective response rate by IDH1 mutation status; duration of response; clinical benefit rate; overall survival (OS) among subjects with GBM or AA which is IDH1 wild type or mutant; OS at 9, 12, 18, and 24 months; and mean OS. • Revised clinical assessments in accordance with changes to the protocol. • Clarified that the Intent-to-Treat Population (all randomized subjects) is the primary population for efficacy analysis. Added a note that secondary analysis may be conducted on the Efficacy Evaluable Population (all subjects who receive surgical resection and at least one dose of Toca FC or SOC treatment).
Version 3 dated 14 Dec 2017	Revisions based on the amended protocol (Version 6): • Removed reference to Phase 2 portion of the study, as the amended protocol has incorporated a Phase 3 seamless design • Revised null and alternative hypotheses of OS; added sensitivity analyses for the primary endpoint (OS) • Revised secondary objectives to include assessments of durable response rate (DRR), durable clinical benefit rate (DCBR), duration of durable response (DDR), DRR by IDH1 mutation status, and progression-free survival (PFS) rate at 12, 18, and 24 months. • Added analysis for secondary endpoints of DRR, DCBR, DDR, and OS12. Revised multiplicity comparisons for secondary endpoints; will use the Holm's procedure. • Revised sample size estimate based on modified assumptions for standard of care (SOC) control arm per contemporary estimates and Toca 511 and Toca FC arm per more mature preliminary Phase 1 data; increased power from 80% to 85% • As part of the modification of the study design, included 2 interim analyses for the OS endpoint at 50% (129 events) and 75% (193 events) of the total required number of events (257 events) • Added analysis of demographics and baseline disease characteristics between the first set of 187 subjects and subjects enrolled in latter part of the study to assess similarity between the two sets of subjects separated by a pause in enrollment • Added presentation of tumor histology at study entry and central evaluation at time of study surgery • Added subgroup analysis for measurable vs non-measurable tumor at C1D1 • Added analysis of association between OS and DRR • Revised safety presentations • Added analyses of viral safety

Version	Change
Version 4 dated 24 Jul 2018	• Incorporated analyses of safety and efficacy by ethnicity/race (non-Hispanic/Latino vs Hispanic/Latino and White vs non-White) • Added exploratory analyses to evaluate potential delayed treatment effect of OS • Added reference to Imaging Review Charter for assessment of DRR by independent radiology review (IRR). Defined criteria for assessment of clinical status in evaluation of response.
Version 5 dated 12 Nov 2018	• Redefined the tumor response outcomes according to the IRR conducted per the Imaging Review Charter. • Added an exploratory analysis of the DRR-RANO which will be conducted by incorporating the IRR as well as clinical status criteria. • Added an exploratory analysis of the objective response rate (ORR).

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and data displays to be included in the clinical study report (CSR) for Study Tg 511-15-01. This document provides details on study populations and on how the variables will be derived, how missing data will be handled as well as details on statistical methods to be used to analyze the safety and efficacy data for Study Tg 511-15-01.

This document may evolve over time, for example, to reflect the requirements of protocol amendments or regulatory requests. The SAP will be finalized before the database is locked. Deviations from the final approved plan will be noted in the clinical study report.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective is to compare the overall survival (OS) of subjects treated with Toca 511 combined with Toca FC to subjects treated with standard of care after tumor resection for recurrence of glioblastoma (GBM) or anaplastic astrocytoma (AA).

2.2. Secondary Objectives

The secondary objectives are:

1. To evaluate the safety of each arm as administered in this study
2. To compare the durable response rate [DRR] (complete response [CR] or partial response [PR] $\geq$ 24 weeks) between arms
3. To compare the durable clinical benefit rate (DCBR: CR or PR $\geq$ 24 weeks or SD $\geq$ 18 months) between arms
4. To assess the duration of durable response (DDR) of each arm
5. To assess overall survival (OS) and DRR by isocitrate dehydrogenase 1 (IDH1) mutation status
6. To compare overall survival at 12 months (OS12) between arms
7. To compare the patient reported outcome and quality of life between arms
8. To compare progression-free survival (PFS) rate at 12, 18, and 24 months between arms

3. STUDY DESIGN

This is a multicenter, randomized, open-label study of Toca 511 and Toca FC versus SOC that comprises Investigator's choice of single agent chemotherapy (lomustine or temozolomide) or bevacizumab administered to subjects undergoing resection for first or second recurrence (including this recurrence) of GBM or AA. Subjects meeting all of the inclusion and none of the exclusion criteria will be randomized at the time of surgery in a 1:1 ratio to receive either Toca 511 and Toca FC (Experimental arm, Arm T), or control treatment with one option of standard of care (Arm SOC). Due to the prognostic influence of molecular subgroups such as IDH1 mutation, the trial will be stratified based on this determination from the primary pathology or subsequent biopsy known locally. A recent biopsy for this determination is not required for this study. A second stratification factor is based on the subject's Karnofsky Performance Status (KPS) (70-80 vs 90-100). Further, to account for potential differences in treatment choices for the control arm in regions, the trial will be stratified by geographical region (United States, Canada, Ex-North America) during the randomization process.

This study will use a volume of Toca 511 of 4 mL. This amount of virus is within the dose found safe and well tolerated in the previous studies. Toca 511 will be administered once by making multiple injections into the walls of the resection cavity immediately following resection.

This study will use a dose of 220 mg/kg/day for 7-day courses of oral Toca FC beginning approximately 6 weeks after tumor resection and repeated every 6 weeks. Subjects may continue taking Toca FC until the investigator decides that no further benefit can be derived from treatment or intolerance.

Since there are various treatment alternatives for recurrent GBM or AA, investigators may choose any of the single agent treatments for subjects randomized to the SOC arm listed in Table 1 for the control treatment arm. When selecting the treatment, investigators will take into consideration the subject's prior treatment and clinical status following surgical resection of the tumor.

Table 1: Investigator's Choice Single Agent Treatments (SOC Arm)

Singe Agent Treatment	Dose
Lomustine	(Oral [PO]) 110 mg/m^2 repeated every 6 weeks
Temozolomide	(PO or IV) Initial dose of 150 mg/m^2 once daily for 5 consecutive days per 28-day treatment cycle, may be increased to 200 mg/m^2 once daily for 5 consecutive days in the following 28-day treatment cycles
Temozolomide metronomic	(PO) 50 mg/m^2 once daily continuously
Bevacizumab	(IV) 10 mg/kg every two weeks

IV = intravenous; PO = oral (administration)

This study will enroll approximately 380 subjects with GBM or AA whose tumor has recurred or progressed following first-line therapy. Subjects with known methylated O6-methylguanine-DNA methyltransferase (MGMT) promoter must have received first-line therapy with resection, followed by temozolomide and radiotherapy (given concurrently in subjects with GBM). Subjects with known unmethylated MGMT promoter must at least have received resection followed by radiation. Subjects to be studied must have elected to undergo repeat resection.

3.1. Treatment Assignment

Subjects will be randomized at the time of surgery in a 1:1 ratio to receive either Toca 511 and Toca FC, or control treatment. Subjects will be stratified according to: (1) geographical region (United States vs Canada vs Ex-North America), (2) IDH1 mutation status (present [mutant] vs absent [wild type]), and (3) KPS (70-80 vs 90-100).

The randomization code will be generated by an independent vendor and incorporated to a centralized randomization system, which will also be used to communicate subject randomizations to study sites through an Interactive Web Response Service (IWRS) within the electronic data capture system. All randomized subjects will have both a unique subject identifier and a unique random code identifier. No random code identifiers are to be reused once assigned.

3.2. Sample Size Justification

The assumed median OS for subjects in the control arm is 9.8 months (Reardon 2017), and the median OS for subjects in the Toca 511 and Toca FC arm is 14.3 months (based on preliminary Phase 1 data). With an assumed active enrollment duration of 28 months and an additional 18 months of follow-up, a sample size of approximately 380 subjects in total is planned to achieve the required number of death events (257 events) to detect a hazard ratio (HR) of 0.685 at a two-sided alpha of 0.05 and a power of 85%. The sample size was calculated using East® 6.4.

4. INTERIM ANALYSES

For the OS endpoint, 2 interim analyses and 1 final analysis are planned for this study after observing approximately 50% (129 events) and 75% (193 events) of the total required number of events (257 events; Table 3). The OS endpoint will incorporate group sequential design with the O'Brien-Fleming boundaries as implemented by Lan-DeMets alpha spending method. This method ensures that the type I error rate is not inflated. The alpha spends for OS are 0.0031 and 0.0162 for the first and second interim analysis, respectively. The exact significance levels will be determined according to the observed number of events at the time of analysis. At the time of the first interim analysis of OS, it is anticipated that all 380 subjects would have been enrolled into the study.

Table 2: Statistical Operating Characteristics for OS (α = 0.05)

	Interim Analysis 1 (~50% of total events)	**Interim Analysis 2 (~75% of total events)**	**Final Analysis (Total of 257 events)**
Number of death events	129	193	257
Projected time to analysis from FPI (months)	30	38	46
Incremental α spend	0.0031	0.0162	0.0307
Hazard Ratio (efficacy)	≤ 0.59	≤ 0.71	≤ 0.78

FPI = first patient in

5. DEFINITIONS AND CONVENTIONS

This section addresses the definitions, algorithms, and conventions that will apply to the analysis and handling of the data in general. Rules that are data specific will be addressed in the detailed footnotes of individual summary tables.

5.1. General Summary Table and Individual Subject Data Listing Considerations

Summary tables and listings (ie, post text tables and individual subject data listings) are prepared according to International Conference on Harmonization (ICH) Guideline E3 Structure and Content of Clinical Study Reports and include a "footer" providing explanatory notes that indicate at a minimum:

- Date of data extraction;
- Date of output generation;
- SAS program name, including the path that generates the output; and
- Any other output specific details that require further elaboration.

Post text tables also include reference(s) to the subject data listing(s) that supports the summary data. The data extraction date links the output to the archived database that is locked to ensure the replication of the results.

Summaries of study population and baseline characteristics will include a total column. Unless otherwise noted, all SOC treatments will be combined into a single arm, labeled SOC. The order of drug presentation will be Toca 511 and Toca FC first followed by the combined SOC group. The summary tables clearly indicate the number of subjects to which the data apply, and unknown or not performed are distinguished from missing data. Summary tables for medications and medical conditions are coded according to the World Health Organization (WHO Drug Version September 2015, enhanced) dictionary. Adverse event (AE) and medical history preferred terms and body/organ systems are coded using the Medical Dictionary for Regulatory Activities (MedDRA, Version 20.1 or later). Supportive individual subject data listings, at a minimum, are sorted and presented by treatment arm and investigational site. Listings also include subject number, visit number, visit date, and days relative to randomization date. No imputations are imposed for missing clinical data. Handling of missing or partial dates and treatment emergent flags are discussed in Section 7.5.1 and Section 9.2.

5.2. Calculations Using Dates

In general, study Day 1 will be defined as the date of randomization. Then for all clinical assessments, study days will be calculated as: assessment date − randomization date + 1.

Overall survival will be defined in months as: (date of death or last date known to be alive − randomization date + 1) / 30.4375. Progression-free survival will be defined in months as: (date of progression or death or last assessment date – randomization date + 1) / 30.4375.

Age for all subjects will be calculated as the truncated difference (ie, the fractional part will be ignored) between the date of informed consent and the subject's birth date (DOB) adjusted for years: age = int[(date of informed consent – DOB)/365.4375].

Duration of hospital stay defined in days will be calculated as the difference between the admission and discharge dates plus 1 day.

5.3. Baseline

The endpoints of overall survival and PFS will be assessed from time of randomization; the evaluation of disease progression (eg, PFS) or disease response (eg, DRR) will be assessed relative to Cycle 1 Day 1 (C1D1), prior to study treatment of Toca FC or SOC.

Changes in safety endpoints may be assessed separately from:

- The measurement (screening) reported prior to surgery; and
- The measurement reported prior to the first dose of Toca FC or SOC therapy at C1D1.

5.4. Visit Windows for Analysis

Visit windows will be created for analysis, to include data collected at unscheduled visits. Visit windows will apply to all treatment arms. Although the treatment regimen may be different across arms, the data collection over time is expected to be collected in 6 week intervals (ie, 42 days). Therefore, visit windows are designed to correspond to analysis visits at 6-week intervals after C1D1.

When multiple visits occur within the same window, the visit closest to the target day will be selected. When two visits are equidistant from the target day, the visit occurring latest in the window will be retained for analysis.

Refer to Table 3 for the assessment visits per the schedule of events (SOE) and corresponding relative target day and visit windows. An analysis visit is provided for two definitions of baseline: the measurement reported prior to surgery on Week 1 Day 1 (W1D1), and the measurement reported prior to systemic treatment at C1D1. The post-baseline analysis visit refers to visit labels that will be presented in tabular summaries of data and is given in time relative to C1D1, to match the scheduled frequency of data collection in the SOE (ie, every 6 weeks).

Table 3: Visit Windows (Experimental and SOC Arms)

Time Point	Analysis Visit	Relative Target Day	Visit Window (Days)
Screening	Screening	N/A	Last measurement reported prior to surgery at W1D1 (ie, Screening measurement or unscheduled if collected between Screening and W1D1)
C1D1	C1D1	1	Measurement prior to the first administration of Toca FC or SOC treatment
Analysis Interval 1	6 Weeks (Post C1D1)	42	22 – 63
Analysis Interval 2	12 Weeks (Post C1D1)	84	64 – 105
Analysis Interval 3	18 Weeks (Post C1D1)	126	106 – 147
Analysis Interval 4	24 Weeks (Post C1D1)	168	148 – 189
Analysis Interval 5	30 Weeks (Post C1D1)	210	190 – 231
etc			

These visits will continue, measured in weeks at 6-week intervals post C1D1, for as long as subjects are completing the scheduled visits per the SOE. Beginning with C1D1, the difference in the relative target day from one visit to the next is 42 days (ie, 6 weeks). Visit windows are intended to be contiguous such that all data collected at all post-baseline visits, whether scheduled or unscheduled, will map to one of the visits. Visit windows are inclusive of the start and stop date of the interval and each interval after C1D1 spans 42 days.

Viral testing data will be summarized from Week 1 post-surgery up to 5 years since the Toca 511 administration date for the Experimental arm only. The subject listing of viral testing data will be provided for subjects surviving more than 5 years relative to the Toca 511 administration date. Visit windows for viral testing summary are presented in Table 4.

Table 4: Visit Windows for Viral Testing Data Analysis (Experimental Arm)

Analysis Visit	Target Day Relative to EOT	Visit Window Relative to EOT (Days)
W1 post-surgery	NA	NA
C1D1 prior to the first administration of Toca FC	NA	NA
C2D1	NA	NA
C4D1	NA	NA
C8D1	NA	NA
C12D1	NA	NA
C16D1	NA	NA
Year 0.5	182	133-273
Year 1	365	274 – 456
Year 1.5	547	457– 638
Year 2	730	639 – 821
Year 2.5	912	822 – 1003
Year 3	1095	1004 – 1186
Year 3.5	1277	1187– 1368
Year 4	1460	1369– 1551
Year 4.5	1642	1552– 1733
Year 5	1825	1734 – 1916

Viral testing collection dates will be mapped to the analysis visits based on days relative to the end of treatment (EOT). When multiple visits occur within the same window, the highest quantitative value (ie, worst value) will be retained for analysis. All data will be listed.

5.5. Analysis Populations

5.5.1. Screen Failures

Screen failure subjects will be included in the database, to include the reason for the screen failure.

5.5.2. Safety Population

The Safety Population includes all randomized subjects who receive surgical resection. Assignment of subjects to treatment arm is based on the treatment actually received.

5.5.3. ITT Population

The Intent-to-Treat (ITT) Population includes all randomized subjects, and is the primary population for efficacy analysis. Assignment of subjects to treatment arm is based on the treatment randomized.

5.5.4. Efficacy Evaluable Population

The Efficacy Evaluable Population includes all subjects who receive surgical resection and at least one dose of Toca FC or one dose of SOC prior to EOT. The subjects will be classified according to their assigned treatment arm irrespective of the actual treatment received. The Efficacy Evaluable population will be used as sensitivity analyses for the primary endpoints.

5.5.5. Handling of Dropouts or Missing Data

Every effort will be made to determine each subject's progression and survival information. However, subjects may withdraw their consent at any time from further participation in the study. Subjects may withdraw consent from treatment, survival follow-up, or both. Withdrawal of consent from treatment and withdrawal of consent from survival follow-up will be reported separately.

In analyses presented over time by visit, no imputations will be performed on missing data. All analyses will be based on observed data only. The effective sample sizes at each assessment visit will be based on the total number of subjects with non-missing data for the parameter of interest at that visit.

Unless otherwise specified, the following general imputation rules will be used for missing date in the assessment of an event:

- If all parts of the date are missing, the date will not be imputed. In the case where only the start day of an event is missing, it will be replaced by the start day of study treatment if the event occurs in the same month and year. Otherwise, it will be replaced by the first of the month. If the stop day is missing, the stop day of the event will be replaced by the stop day of study treatment. Otherwise, the last day of the month will be used to replace the missing stop day.
- If both the start day and month of an event are missing, the start day and month will be replaced by the start day and month of study treatment if the event and the start of the treatment occur in the same year; otherwise, it will be replaced by 1st of January.

All imputed dates have to be prior to the dates of withdrawal of consent, lost to follow-up, and death.

6. SUBJECT ACCOUNTING

6.1. Subject Disposition

Distribution of subjects by treatment arm for each of the analysis populations will be provided. In addition, the number of subjects in the ITT Population will be summarized by study site and treatment arm. The number and percentage of subjects who fail screening will also be presented by the reason for screen failure.

Treatment discontinuation will be summarized according to reasons of discontinuation as documented in the case report form (CRF) (ie, consent withdrawal, AE, etc). Similarly, reasons for end of study will be summarized.

6.2. Protocol Deviations

Major protocol deviations will be summarized by treatment arm and all subjects treated for the ITT population. All protocol deviations will be determined and appropriately categorized prior to database lock. The number and percentage of subjects with any major protocol deviation as well as the number and percentage of subjects with deviations within each category will be summarized.

6.3. Study Treatment and Extent of Exposure

Study treatment duration in months will be based on the Drug Accountability and EOT/PD CRFs determined as (end of treatment date–date of first dose date+ 1) / 30.4375.

For Toca 511, descriptive summary on the total volume injected, number of injections, and total dose in transducing units (TU) will be presented. Transducing units will be calculated as follows:

$$\text{TU} = \text{Strength of Toca 511 Administered (TU/mL)}^{\dagger} \times \text{Total Volume Injected (mL)}$$

† A standardized strength of 3.3×10^8 TU/mL is imputed.

For Toca FC, an overall summary (n, mean, s.d., median, min, max) of the number of cycles initiated and a by cycle summary of the number and percent of subjects initiated each cycle of Toca FC (ie, drug was dispensed) will be presented. The number and percentage of subjects who completed the specified range of Toca FC tablets, starting at ≥ 80% compliance to a maximum of 100% in increment of 5%, will be summarized. The percentage will be the ratio of the number of tablets dispensed - the number of tablets returned divided by the total number of tablets dispensed x 100%.

Reason for dose change in the Toca FC will also be presented. A summary of the number and percent of subjects whose dose was changed due to a change in serum level, the reporting of an AE, weight change, or other reasons, will be presented (note that if a subject reported more than one reason for change in dose, the subject will be counted for each reason).

For the control arm, an overall summary of the number of cycles initiated and a by cycle summary of the number and percent of subjects initiated each cycle (ie, drug was administered/taken) will be presented. Additionally, a summary table presenting the actual total

dose received (bevacizumab [mg/kg], lomustine [mg/m^2], and temozolomide [mg/m^2]) will be included for each drug separately.

A descriptive summary of the median total daily dexamethasone (or equivalent) dose received while on treatment will be presented by cycle. A plot on the median dose received across cycles will also be included.

The individual subject data listing will provide dosing information for each cycle that comes from a derived dataset constructed from the Toca FC, metronomic temozolomide, temozolomide, lomustine, and bevacizumab CRF pages. A listing of Toca 511 and Toca FC lot numbers allotted to subjects will also be presented.

7. BASELINE SUBJECT DATA

7.1. Demographic and Baseline Disease Characteristics

Demographic and baseline variables including age, sex, ethnicity and race, will be summarized by treatment arm and all subjects combined for the ITT. Age will be calculated relative to date of informed consent and will be summarized using descriptive statistics as well as by the number and percent of subjects in age categories (< 65, ≥ 65 years). Similarly, height and weight will be summarized using descriptive statistics. Sex, ethnicity and race, and geographical region will be summarized with the number and percent of subjects in each parameter category.

Baseline disease characteristics include KPS category (70-80 vs 90-100), IDH1 mutation status (mutant vs wild type), tumor histology (GBM vs AA), number of recurrences, and region. Baseline characteristics will be summarized for the ITT by treatment arm and all subjects combined.

The demographics and baseline disease characteristics between the first set of 187 subjects randomized into the Phase 2 portion of the study and the subjects enrolled in the latter part of the study will be provided to assess the similarity in the two sets of subjects separated by a pause in enrollment.

7.2. Listing of Subject Inclusion and Exclusion Criteria

Inclusion and exclusion criteria will be provided in a data listing by subject.

7.3. Neuro-Oncology History

Neuro-oncological history will be summarized for the following variables, relative to the initial diagnosis of the underlying disease:

- Time (months) since initial diagnosis and time (months) since initial surgical resection
- Tumor histology
- Type of procedure, use of Gliadel wafer
- Duration (months) of postoperative radiation therapy and total therapy delivered during radiation treatment (cGy)
- Prior use of temozolomide (yes/no) and time (months) since last dose of temozolomide
- Prior use of bevacizumab (yes/no)

Prior use of neuro-oncology treatments will be summarized by Sponsor-defined category of treatment. MGMT promoter methylation status at initial diagnosis and central evaluation results at time of study surgery will be summarized separately. Tumor histology at time of study entry and central evaluation results at time of study surgery (see Section 8.3) will also be summarized separately.

7.4. Medical History

Subject medical history, to include recording of past and present illnesses at screening, will be provided in a subject data listing.

7.5. Prior Medication History and Medications Present at Entry

All medications, both prior and concomitant, will be coded with respect to the anatomic-therapeutic-class (ATC) coding system and the data summarized by preferred term (ie, generic name) and major and minor drug classes. A prior medication is defined as any medications administered prior to the date of surgery.

7.5.1. Missing and Partially Missing Start and Stop Dates

See Section 5.5.5 for the general imputation rules for missing dates.

7.6. Concomitant and Other Medications

Medications entered on the case reports forms will be mapped to the ATC drug class and generic drug name. A concomitant medication is defined as any medication administered on or after the surgery date. Prior and concomitant medications will be summarized separately; concomitant medications will be summarized in a similar manner as prior medications described in Section 7.5.

7.6.1. Missing and Partial Concomitant and Other Medication Start and Stop Dates

See Section 5.5.5 for the general imputation rules for missing dates.

8. EFFICACY

8.1. General Considerations

In general, quantitative variables will be summarized to indicate the population sample size (N), number of subjects with available data (n), mean, s.d., minimum, and maximum values. Qualitative variables will be summarized by the population size (N), number of subjects with available data (n), number of subjects in each category, and the percentage of subjects in each category. Unless otherwise noted, the denominator to determine the percentage of subjects in each category will be based on the number of subjects with available data.

8.2. Statement of the Null and Alternate Hypotheses

The null and alternative hypotheses in testing of OS are as follows:

- H_o: For subjects randomized to Toca 511 and Toca FC arm relative to subjects randomized to SOC arm, $S_T(t)=S_C(t)$, for all $t>0$
- H_A: For subjects randomized to Toca 511 and Toca FC arm relative to subjects randomized to SOC arm, $S_T(t)\neq S_C(t)$, for some $t>0$

where $S_T(t)$ and $S_C(t)$ are the survival distributions for subjects treated with Toca 511 and Toca FC, and SOC respectively.

8.3. Subgroup Analyses

The primary endpoint of OS will be examined for the following subgroups:

- Age (< 65, ≥ 65 years)
- Gender (females, males)
- Ethnicity (non-Hispanic/Latino, Hispanic/Latino)
- Race (White, non-White)
- IDH1 mutation status (mutant, wild type)
- KPS (70-80, 90-100)
- Region (United States, Canada, Ex-North America) [Note: Regions from Canada and Ex-North America may be pooled if the sample size in each region is small]
- GBM (yes, no) at study entry collected from Neuro-oncology CRF page (ie, Glioblastoma worst grade in tumor histology at initial diagnosis, recurrence, or at study entry)
- MGMT methylation status (methylated, unmethylated) from central evaluation
- Number of recurrences (first or second)
- Baseline steroid use (yes/no)

- Extent of resection by independent radiology review (IRR) (complete vs incomplete)
- Measurable vs non-measurable tumor at C1D1

A forest plot presenting the HR that compares Toca 511 and Toca FC with SOC for OS will be presented for overall and for each of the subgroup categories listed above. A forest plot presenting the relative risk may be generated for the DRR endpoint, presented for overall and for each subgroup.

8.4. Multiple Comparisons and Multiplicity

Treatment arms will be compared for each of the following secondary endpoints using the Holm's procedure:

1. Durable response rate (DRR)
2. Durable clinical benefit rate (DCBR)
3. Duration of durable response (DDR)
4. Survival rate at 12 months (OS12)

All confidence intervals will be two-sided 95% confidence intervals and inferential statistical analyses will be evaluated with an overall significance level of alpha = 0.05 (two-sided) unless otherwise specified.

8.5. Other Endpoints

The other endpoints include PFS, the subscales from the European Organization for Research and Treatment of Cancer (EORTC) core Quality of Life Questionnaire C-30 (QLQ-C30), the Quality of Life Questionnaire Brain Cancer Module (EORTC QLQ-BN20), and the health economic endpoints including the number of hospitalizations and duration of hospitalization. No multiplicity adjustment is planned for these endpoints.

8.6. Analysis of the Primary Efficacy Endpoint

The primary analysis population is the ITT Population. The primary efficacy endpoint is OS. For OS, all death events will be considered in the analysis. Subjects with no documentation of death will be censored at the last date known to be alive, per the data collection. The null and alternative hypotheses are stated in Section 8.2.

The Kaplan-Meier method will be employed to estimate the survival functions, using time to death and a censoring variable, and Kaplan-Meier curves will be plotted.

A stratified log-rank test will be used to compare the Toca 511 and Toca FC arm with SOC arm. The median and 25^{th} and 75^{th} percentiles will be estimated and their corresponding 95% confidence intervals (CIs) using the Kaplan-Meier estimates, as well as respective descriptive statistics. The standard error will be estimated using Greenwood's formula (Greenwood 1926) for time points for overall survival at 9, 12, 18, etc, months. Stratification factors for IDH1 mutation (mutant vs wild type), KPS category (70-80 vs 90-100), and geographical region

(United States, Canada, Ex-North America) will be employed. Statistical inference will be evaluated in the context of the group sequential testing design described in Section 4.

Results of the primary efficacy endpoint, OS, will be presented by treatment arm (Toca 511 and Toca FC, followed by SOC), including the counts and percentages for number of subjects who died or are still alive.

Sensitivity analyses on the primary endpoint will be performed to assess the robustness and consistency of the endpoint. Sensitivity analysis using non-stratified analysis (eg, non-stratified log-rank test) will be performed as supportive analysis. The primary endpoint will also be analyzed using the Efficacy Evaluable population. If the number of subjects is small in one or more of the regions, these regions may be pooled to form a larger region (eg, pooling Canada and Ex-North America into a single stratum).

If the proportional hazards assumption is violated for the OS endpoint and warrant additional analysis, the following methods may be performed:

- restricted mean survival time (RMST) test (Uno 2014, Royston 2011)
- time-dependent covariate analysis

The methodology proposed by Xu et al (Xu 2016, Karrison 2016) may be performed in the event that there is a delayed treatment effect resulting in a delayed separation of the survival curves. The weighted log-rank statistic may also be explored to further evaluate the impact of the delayed effect. In addition, a 9-month landmark analysis for OS may be performed using method described in Anderson, 1983. A 9-month landmark was selected based on prior reports that suggest this time point may be meaningful for assessing survival in this patient population (Taal 2014, Wick 2010).

The results from these analyses will not be adjusted for multiplicity testing. Each analysis will be compared at a significance level of 0.05.

8.7. Analysis of the Secondary Efficacy Endpoints

Secondary endpoints will be analyzed for the ITT Population.

For the DRR endpoint, the Cochran-Mantel-Haenszel (CMH) test will be used to test the hypothesis; a Chi-square test may be performed if appropriate. For DRR, subjects with missing outcome will be assumed as non-responders. The relative risk (treatment:control) along with its associated confidence intervals will be presented. To assess the durability of response, approximately 18 months of follow-up is necessary to allow a mature analysis of durable response rate (CR or PR $\geq$ 24 weeks). Therefore, the DRR assessment may utilize the first set of 187 subjects randomized into the Phase 2 portion of the study based on the current projection of the OS endpoint. The DRR assessment will be based on the IRR conducted per the Imaging Review Charter. An exploratory analysis of the DRR-RANO will be conducted by incorporating the IRR as well as clinical status criteria defined in Section 8.7.1.

The durable clinical benefit rate (DCBR) is defined as CR or PR $\geq$ 24 weeks or SD $\geq$ 18 months. This endpoint will be analyzed using the CMH test; a Chi-square test may be performed if appropriate. The DCBR will be assessed similar to the DRR endpoint.

The duration of durable response is defined as time from initial CR or PR to date of PD or death due to PD. If the subject did not experience an event (ie, PD), subjects will be censored at the last date of radiographic scan that showed non-PD. A stratified log-rank test will be used to analyze the endpoint; non-stratified analysis may be performed if appropriate.

The survival rate at 12 months (OS12) will be determined from the Kaplan-Meier curves. The ratio of the survival rate will be computed along with its associated confidence interval.

8.7.1. Determination of Clinical Status in the Evaluation of Response per RANO Criteria

Criteria for the assessment of clinical status in the evaluation of response are provided below.

For KPS, the definition of deterioration by KPS assessment is a decline in KPS score from 80-100 at baseline to 60 or lower, with confirmation at next visit 4 or more weeks apart, or from 70 at baseline to 50 or lower, with confirmation at next visit 4 or more weeks apart.

For steroids use, the following definitions will apply:

- Off steroid is defined as either no steroid or the average steroid dose is $\leq$ 2 mg dexamethasone equivalent (ie, physiologic dose) during the 5 days prior to the MRI scan date.
- Stable steroid is defined as not meeting the definition of increased steroid, or off steroid within the 5 days prior to the MRI scan date relative to the 5 days before C1D1.
- Increased steroid is defined as a $\geq$ 10% increase and a $\geq$ 4 mg increase in the average of the daily doses of steroids taken for the 5 days prior to the MRI scan date, compared with the average of the steroid dose taken for the 5 days before C1D1, where the C1D1 average was above physiologic levels (ie, > 2 mg of dexamethasone or other corticosteroid equivalent).

Comorbid AE is defined as an unrelated Grade 3 or higher adverse event that occurs within one week (7 days) before the MRI.

8.8. Analysis of Association Between OS and DRR

The strength of association between the OS and DRR endpoints will be explored using Cox regression model with DRR as covariate. Additional estimate of the association such as the Kendall's tau statistic may be calculated if warranted.

8.9. Analysis of the Other Endpoints

Additional endpoints will be analyzed for the ITT Population.

Progression-free survival is defined as the time from randomization date to tumor progression based on the modified Response Assessment in Neuro-Oncology Working Group (RANO) criteria as defined in the protocol. Progression-free survival will be based on the IRR conducted per the Imaging Review Charter.

The date of progression or death and the censoring time will be based on the FDA guidance *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics* (May 2007), as defined in Table 5. Baseline for the assessment of progression is defined in Section 5.3.

Table 5: Determining Date of Progression or Censoring for PFS Analysis

Situation	Date of Progression or Censoring	Outcome
No C1D1 tumor assessments	Randomization	Censored
Alive and without documentation of disease progression	Date of last disease assessment	Censored
Treatment discontinuation for undocumented progression	Date of last disease assessment	Censored
Treatment discontinuation for toxicity or other reason	Date of last disease assessment	Censored
Non-protocol anticancer treatment started before documentation of disease progression or death	Date of last disease assessment prior to start of non-protocol anticancer treatment	Censored
Death before first disease assessment	Date of death	Progressed
Death or disease progression between planned disease assessments	Date of death or first disease assessment showing disease progression, whichever occurs first; if death occurs within 6 weeks after the last disease assessment, the death will be considered the event when there was no documented progression prior to death.	Progressed
Death or progression after more than one missed disease assessment	Date of last disease assessment visit without documentation of disease progression that is before the first missed visit	Censored

Progression-free survival will be analyzed using the Kaplan-Meier method. Refer to Section 8.2 for the hypothesis test. The point estimates for the proportion of subjects that are event-free at 6, 9, 12 months and other time points will be presented along with the 95% CI by treatment arm. These estimates will be obtained from the Kaplan-Meier curves.

Health economic endpoints including the number of hospitalizations and duration of hospitalization will be summarized using descriptive statistics by time interval and treatment arm.

The EORTC QLQ-C30 contains both single-item and multi-item scales. Of the 30 items, 24 aggregate into nine multi-item scales representing various health-related quality of life (HRQoL) dimensions – Physical Functioning, Role Functioning, Emotional Functioning, Cognitive Functioning, Social Functioning, Fatigue Symptoms, Pain Symptoms, Nausea Symptoms, and Global Measure of Health Status. The remaining six single-item scales assess individual symptoms. High scores indicate better HRQoL for the global health status and functioning scales, while high scores indicate worse HRQoL for the symptom scales.

The EORTC QLQ-BN20 also contains both single-item and multi-item scales. Of the 20 items, 13 aggregate into four multi-item scales – Future Uncertainty, Visual Disorder, Motor Dysfunction, and Communication Deficit. The remaining single items assess other disease symptoms and treatment toxic effects.

For all these scales, a higher score represents a worse HRQoL. The principle for scoring these scales is the same in all cases – the raw score is calculated by computing the average of the items for each particular scale. A linear transformation will be applied to standardize the raw score so that scores range from 0 to 100; a higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms (Maringwa 2011).

To demonstrate compliance, the number and percent of subjects with an evaluable assessment for each of the EORTC QLQ-C30 and EORTC QLQ-BN20 questionnaires will be presented by time point.

Time to degradation in HRQoL will be defined as the time in months from randomization until a 10-point reduction from baseline (C1D1) within each subscale. Subjects who experience less than a 10 point drop in the scores will be censored at the date of the last QOL assessment. Subjects with missing baseline (C1D1), or subjects with no post-baseline QOL assessment(s) will be censored at the day of randomization. The Kaplan-Meier method will be employed to estimate survival functions, and Kaplan-Meier curves will be plotted. The log-rank statistics will be provided. Counts and percentages of subjects who experienced deterioration, who are censored, as well as the median time to deterioration (TTD) to include the corresponding 95% CI will be presented.

For each subscale within each questionnaire, a mixed effect model for repeated measurement (MMRM) will be implemented to evaluate changes from baseline over time. The dependent variable will be the change from baseline and the model will include fixed effects for treatment arm, time (Analysis Intervals), treatment arm-by-time interaction, and the baseline value. An unstructured covariance model will be used.

For the EuroQol - 5 Dimensions - 5 Levels (EQ-5D-5L), counts and percentages for each categorical response within each domain (Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression) will be summarized. The visual analog scale (VAS) measuring "your health today" will be analyzed separately as a continuous endpoint and interpreted directly as a quantitative measure of a subject's valuation of their own global health status (van Reenen 2015).

An MMRM model will be fit to compare treatment arms for the VAS of the EQ-5D-5L, similar to that described above for the EORTC QLQ-BN20 and EORTC QLQ-C30. Comparisons for the categorical (EQ-5D-5L) summary will be tested using the CMH chi-square statistic with mean scores applied to the ordered categories.

Mean change from baseline (C1D1) results in the subscale scores for EORTC QLQ-BN20 and EORTC QLQ-C30 and the VAS of the EQ-5D-5L will be plotted over time.

8.10. Exploratory Endpoints

Immune monitoring and genomic data may be analyzed using a multivariate model, with a summary provided in a separate report.

Exploratory analyses of durable response rate per RANO (DRR-RANO) will be conducted by defining the tumor response outcomes based on the IRR and clinical status criteria defined in Section 8.7.1.

Objective response rate (ORR) will also be summarized based on the IRR conducted per the Imaging Review Charter.

8.11. Summary of Reasons for Efficacy Non-evaluability/Exclusion from Efficacy Analyses

The reasons for excluding subjects from the Efficacy Evaluable Population will be summarized by treatment arm and supported by an individual subject data listing.

9. SAFETY

Safety analysis will be carried out for the Safety Population, which includes all randomized subjects who receive surgical resection. All AE summaries by treatment arm will be restricted to treatment-emergent AEs (TEAEs), which are defined as those AEs that occurred after surgery and those existing AEs that worsened during the study, up to 30 days post-EOT.

9.1. Overall Summary of Safety

Overall summary of study drug tolerability will be presented by treatment arm to include:

- Number and percent of subjects with TEAEs, including drug related TEAE
- Number and percent of subjects with Grade 3-4 TEAE, including drug-related TEAE
- The number and percent of subjects with serious TEAEs, including drug-related TEAE and Grade 3-4
- The number and percent of subjects with TEAE leading to treatment discontinuation, including drug-related TEAE
- The number and percent of subjects with TEAE leading to death, including drug-related TEAE
- All deaths within 30 days of last dose, including the reasons leading to death

A summary of safety by subgroups based on age (< 65 and ≥ 65 years of age) and ethnicity and race (non-Hispanic/Latino and Hispanic/Latino; and White and non-White) will be presented.

An overall summary of safety for the long-term follow-up post-EOT will be presented.

9.2. Adverse Event Preferred Term and Body/Organ System Summary Tables

Verbatim terms on case report forms will be mapped to preferred terms and system organ classes using the MedDRA dictionary.

9.2.1. Summaries of Adverse Event Incidence Rates for All Subjects

The primary presentation of AEs will be prepared without regard to causality or relationship to study medication and will classify events using MedDRA with respect to preferred term and body/organ system by treatment arm and for all subjects who received surgery. The severity of AEs will be graded on a scale of 1-5 according to the National Cancer Institute (NCI) Common Toxicity Criteria Adverse Events (CTCAE) v4.03. When summarizing by toxicity grade, subjects will be counted once at the body system level (or cluster term level) and once for each applicable preferred term for the most severe event reported; multiple occurrences of the same preferred term for a subject will be counted only once.

Additional summaries of adverse events will be provided as incidence tables (number of subjects experiencing an event) by treatment arm:

- All incidence of TEAEs
- TEAEs by system organ class, preferred term, and toxicity grade
- Grade 3-4 TEAE by system organ class and preferred term
- Most frequent (≥ 5%) Grade 3-4 TEAEs by system organ class and preferred term
- TEAEs leading to dose reduction by system organ class, preferred term, and toxicity grade
- TEAEs leading to death
- Summary of all deaths
- Most frequent (≥ 10%) TEAEs by system organ class, preferred term, and toxicity grade
- TEAEs occurring between surgery and prior to the first dose of Toca FC or SOC by system organ class, preferred term, and toxicity grade
- TEAEs of special interest by system organ class, preferred term, and toxicity grade
- Most frequent (≥ 5%) TEAEs of special interest by preferred term and toxicity grade
- TEAEs of special interest leading to treatment discontinuation
- Serious TEAEs by system organ class, preferred term, and toxicity grade
- Serious TEAEs occurring between surgery and the first dose of Toca FC or SOC by system organ class, preferred term, and toxicity grade
- Serious TEAEs of special interest occurring between surgery and the first dose of Toca FC or SOC by system organ class, preferred term, and toxicity grade
- TEAEs leading to treatment discontinuation by system organ class and preferred term
- Listing of serious TEAEs
- Listing of all deaths
- Listing of TEAEs leading to death

- Listing of deaths within 30 days post-EOT
- Listing of TEAEs leading to treatment discontinuation

Unique information included in the subject data listing will contain AE onset and resolution dates; serious AE (SAE) designation; and body system, preferred term, the verbatim term, the event severity and relationship to study medication, action taken, and outcome.

An incidence table of TEAEs of special interest will also be summarized.

9.2.2. Viral Safety

Viral safety will be presented as follows:

- Incidence of TEAEs by MedDRA system organ class, preferred term, and highest CTC toxicity grade, by severity for subjects with quantitative viremia (qRT-PCR result > BLOQ); subjects with quantitative viremia > 50,000 copies/mL; and subjects with no quantitative viremia (ie, below the limit of quantitation [BLOQ])
- Incidence of TEAEs related to Toca 511 by MedDRA system organ class, preferred term, and highest CTC toxicity grade, by severity for subjects with quantitative viremia (qRT-PCR result > BLOQ); subjects with quantitative viremia > 50,000 copies/mL; and subjects with no quantitative viremia (ie, BLOQ)
- Incidence of TEAEs occurring near (± 2 weeks) the peak of quantitative values

9.3. Extent of Exposure and Compliance

The total dose received (mg) for each study treatment will be calculated based on the Drug Accountability CRFs.

Total dose received for the SOC treatments will be taken from the Drug Accountability CRFs actual total dose.

Compliance will be determined as the total number of tablets dispensed minus the total number of tablets returned, divided by the total number of tablets dispensed, multiplied by 100.

9.4. Toca FC Serum Concentration

Dose reduction for Toca FC will be adjusted on the basis of tolerability (gastrointestinal and constitutional symptoms) and hematologic toxicity. A complete blood count (CBC) will be performed at the beginning of each cycle. Subjects who have Grade 3 or higher anemia, neutropenia or thrombocytopenia, should have a local CBC performed prior to beginning their next cycle of Toca FC.

For each subject in the experimental arm, the 5-FC serum concentration will be tested in Cycle 1 during this study. The Investigator may also determine the serum concentration during any cycle in which he/she is concerned about compliance or side effects.

The 5-FC serum concentration for Cycle 1 will be summarized for the Experimental arm. Descriptive statistics will be presented. Any ad hoc testing due to dose change or relevant toxicity and compliance will be listed.

9.5. Physical Examination

Body systems will be recorded as "normal" or "abnormal" during the physical examination.

9.6. Neurological Examination

Using a 5-point Likert Scale (5=Definitely better, 4=Possibly better, 3=Unchanged, 2=Possibly worse, 1=Definitely worse), mean overall neurological status compared to C1D1 at each post-C1D1 assessment will be summarized by treatment arm.

In addition, neurological examination will be classified as "normal" or "abnormal" by domain (mental status, cranial nerves, motor, sensory, and cerebellar/gait). Two-by-two contingency tables will be presented to summarize the shift from C1D1 to each post-C1D1 time point by domain. Summary results will include the count and percentage of subjects within each shift category and treatment arm. Percentages within each category will be based on the number of subjects with C1D1 value and a non-missing value at the post-C1D1 time points within each domain.

9.7. Vital Signs

Vital sign parameter measurements will be summarized by treatment arm. Descriptive statistics will be presented for results and change from C1D1 at each post-C1D1 time point where parameters were scheduled to be collected per the SOE.

9.8. Karnofsky Performance Status

Karnofsky performance status will be summarized if subject is improved or worsened by comparing to the screening with the C1D1 prior to Toca FC or SOC and EOT.

9.9. Anti-Cancer Therapy

Subsequent use of anti-cancer therapy will be defined as any therapy reported on the Anti-Cancer Therapy form. Subsequent use of anti-cancer therapy will be summarized for those subjects who received any subsequent therapy.

9.10. Dexamethasone Dose

An increase in steroids is defined as a $\geq$ 10% increase and a $\geq$ 4 mg increase in the dexamethasone equivalents for the sum of the daily doses of steroids taken for the 5 days before the current magnetic resonance imaging (MRI) scan compared with the sum of the daily doses of steroids taken for the 5 days before the C1D1 MRI scan.

A decrease in steroids is defined as the case where the sum of the daily doses of steroids taken for the 5 days before the current time point is less compared with the sum of the daily doses of steroids taken for the 5 days before C1D1. Neither increase nor decrease will be defined as stable. The steroid increase, decrease or stable will be summarized at each time point compared to C1D1 by treatment arm.

Time to discontinuation of steroid therapy will be defined as the time (months) from surgery (ie, Day 2 of surgery) to the time of the stop date of the steroid therapy (ie, no more steroid

taken) through EOT, based on entries into the CRF. Time to discontinuation of steroid therapy will be summarized using Kaplan-Meier estimates by treatment arm. The number and percentage of subjects who return to dexamethasone dosing after discontinuation will also be summarized.

9.11. Routine Laboratory Data

All descriptive summaries of laboratory results will utilize data collected at the central laboratory.

Laboratory parameters will be summarized using descriptive statistics at screening and at each post-screening time point by arm. Changes from screening will also be summarized. In addition, change from C1D1 prior to first dose of Toca FC or SOC will also be summarized.

Alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, Potassium, Sodium, HGB, WBC, platelets, ANC, absolute lymphocytes, creatinine, and total bilirubin will be classified according to NCI CTCAE, Version 4.03. Worst shift tables will be provided for these parameters to assess changes in CTCAE grades from screening and shift from C1D1 prior to first dose of Toca FC or SOC. Lab measurements with CTCAE toxicity Grade 3 or 4 will be listed by subject, laboratory test, and unit.

An assessment of incidences of elevations in liver-related laboratory parameters will be performed. The count and percentage of subjects with post-baseline laboratory measurements that meet various criteria, according to FDA guidance *Drug Induced Liver Injury: Premarketing Evaluation* (July 2009), will be summarized for the Safety Population by treatment arm.

9.12. Other Safety Labs – Experimental Arm Only

For summary of viral testing results, there will be two categories of results: (1) BLOQ or (2) with quantitative values, in qPCR or qRT-PCR. Viral DNA and RNA as determined by qPCR (copies/μg) and qRT-PCR (copies/mL), respectively, will be summarized using descriptive statistics by time point for subjects with Quantitative results only and, in addition, peak qPCR and peak qRT-PCR will be included in the same table.

Results of viral shedding (urine and saliva testing) will be presented in a by-subject data listing. Individual subject levels of qPCR and qRT-PCR will be plotted over time.

Viral testing data will be summarized for the first 5 years since the date of administration of Toca 511, and will be listed for subjects surviving more than 5 years.

Antibody change from baseline over time will also be provided in a listing.

9.13. Deaths

Deaths will be summarized by treatment arm with cause of death (eg, disease under study, AE, unknown, or other) presented.

9.14. Surgery

Estimated percentage of tumor resection at surgery will be summarized using counts and percentages of subjects by treatment arm based collection on the Surgery form using the

following categories: complete resection of enhancing disease (ie, estimated percentage of tumor resection reported as 100%), incomplete resection of enhancing disease (ie, percentage of tumor resection reported < 100%), and other (ie, missing entry). Categories will also be summarized based on reporting by the IRR.

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