PROTOCOL TITLE: A Phase I study of subcutaneously administered natural progesterone for the treatment of recurrent GBM

WINSHIP PROTOCOL #: Winship5184-20

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REVISION HISTORY

Revision #	Version Date	Summary of Changes
1	04/12/2022	Removed mention of day 4 PK time point and changed PK determination to be done internally rather than by Syneos.
2	09/12/2022	Allowed patients to be on avastin to prevent rebound enhancement that would make results difficult to interpret.
3	02/03/2023	Allowed inclusion of patients who have had complete resection for recurrent enhancing disease and PKs to be done later.
4	02/24/2025	Switched Oncology co-investigator to Will Read and changed dose escalation to a maximum of 75 mg/day from 100 mg/day.

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1. Study Summary

1.1 Synopsys

Title:	**Pilot study of subcutaneously administered natural progesterone for the treatment of recurrent GBM**
Study Description:	This research study is a single arm, pilot phase 1 study, designed to evaluate the pharmacokinetics, safety/tolerability and efficacy of subcutaneously administer natural progesterone in subjects with recurrent glioblastoma (GBM).
Objectives:	**Primary Objectives**: • To determine pharmacokinetics (PK) of natural progesterone given to recurrent GBM patients by subcutaneous injection is consistent with previous determinations made using the aqueous formulation of progesterone (IBSA). • To determine the safety/tolerability of administering daily subcutaneous natural progesterone for the treatment of patients with recurrent GBMs. • To determine the rate of stable disease (SD) or better (PR/CR) at 8 weeks in eligible patients with recurrent GBM treated with daily subcutaneous natural progesterone. **Secondary Objectives:** • To determine and compare the progression free survival of eligible patients with recurrent GBM compared with matched historical controls treated with a range of standard therapies. • To determine and compare the overall survival of eligible patients with recurrent GBM compared with matched historical controls treated with a range of standard therapies. **Exploratory Objective:** • To determine whether progesterone receptor levels within the tumor correlates with response to daily subcutaneous natural progesterone. • To determine if other intrinsic tumor factors (mutations and genomic loss/gains, see S**ection 5.7** for specific details) correlates with response to daily subcutaneous natural progesterone. • To determine if the absolute values or changes in the level of serum biomarkers (see S**ection 5.7** for specific biomarkers) correlates with response to daily subcutaneous natural progesterone. • To determine the quality-of-life (QOL) by validated instruments of eligible patients with recurrent GBM treated with daily subcutaneous natural progesterone and assess whether this differs from historical controls.

Endpoints:	**Primary Endpoint:** • Pharmacokinetic: Plasma progesterone levels at specified time points. • Safety: Adverse events, clinical assessments (eg. vital sign, physical, etc.), clinical laboratory test. • Efficacy: Overall response rate (ORR) per protocol volumetric definition at 8 weeks. **Secondary Endpoints:** • Efficacy: Progression Free survival (PFS) and Overall Survival (OS) • Exploratory: Progesterone receptor expression levels by immunohistochemistry, specified intrinsic tumor factors (genetic/epigenetic changes), levels/changes in specified serum biomarkers before and 4 weeks after treatment with progesterone, QOL assessment by the EORTC Quality of Life Questionnaire-Core 30/Brain Cancer Module-20 (EORTCQLQ30/BN20); M. D. Anderson Symptom Inventory Brain Tumor Module (MDASI-BT).
Study Population:	The patient population consists of **20-32** subjects ≥18 years of age with. Eligible patients must have glioblastoma at 1st to 3rd recurrence with KPS ≥ 60. Recurrent GBM may be managed by surgery (no minimum enhancing disease required). Additional inclusion/exclusion criteria are specified in protocol.
Phase:	Phase I; Pilot
Description of Sites/Facilities Enrolling Participants:	Winship Cancer Institute of Emory University (Atlanta, GA).
Description of Study Intervention:	Patients will receive the following treatment: Aqueous natural progesterone for injection (25-75 mg SC) daily for up to 24 weeks.
Study Duration:	Patients will be treated for up to 24 weeks unless there is unacceptable toxicity, disease progression per protocol specification, or the patient opts to withdraw prior to that time which would result in early drug discontinuation. Patient will be followed at 4 weeks following drug discontinuation for their end of study (EOS) visit.

1.2 Schema

Registration

Confirm patient eligibility. Patients will need to be at ≤ 3rd recurrence of GBM. 20 patients will be treated with natural progesterone (P4) at the final expansion dose. Plan is to enroll up to 32 patients.

⇩

Baseline testing/imaging

Standard brain MRI with and without contrast including perfusion imaging, standard labs (CBC w/differential and complete metabolic panel) and neurologic exam within 14 day window prior to start of therapy.

⇩

Dose finding phase of study

Doses of 25 mg, 50 mg, or 75 mg subcutaneously 1x/day will be assessed. Plan to employ 3+3 design with tolerance of drug determined by DLT in no more than 1/3 of patients (≥ grade 3 toxicity not clearly due to the underlying disease or extraneous causes with exception as noted in **Section 5.3**) within 28 days of starting treatment. Pharmacokinetic assessments will be performed on the first 3 patients at each dose level. (N = 6-12).

⇩

Expansion phase of study

Maximal tolerated dose from dose finding phase (25 mg, 50 mg, or 75 mg) administered subcutaneously 1x/day will be given in this expansion cohort until 20 patients have initiated the dose determined from the dose finding phase. (N = 14-17).

⇩

Duration of therapy and follow up schedule

Therapy will continue until disease progression on MRI or intolerable and/or dose-limiting toxicity. Standard brain MRI with and without contrast including perfusion will be performed at 4 weeks (± 1 week), 8 weeks (± 1 week) and every 8 weeks (± 2 weeks) thereafter unless otherwise clinically indicated based on physician judgement. This imaging schedule will continue on study until there is definitive evidence of progression on MRI or 24 weeks. Patient will be seen in followup for exam every 2 weeks and toxicity assessment weekly for 4 weeks (± 3 days) while on the 1st 4 weeks of drug therapy. Thereafter, followup for exam and toxicity assessment will be at q4week intervals (± 1 week) until patient comes off study for whatever reason (eg. tumor progression, poor tolerance of drug, patient choice, etc.) or 24 weeks (option for compassionate use beyond 24 weeks off study will be determined on a case by case basis). Lab assessments will be performed at the day 15 and 29 visits (± 3 days) and thereafter q4weeks (± 1 week).

Progesterone dose escalation/de-escalation rules:

Dose Level	Dose of aqueous natural progesterone for injection (mg)
Level -1	25
Level 0	50
Level 1	75

Study will start at Dose Level 0 with dose moving according to the following criteria:

Dose Level -1
- 0 of 3 with DLT → **expand Level -1 to 20 patients**
- 1 of 3 with DLT → 3 more at Level -1
  - 1-2 of 6 with DLT → **expand Level -1 to 20 patients**
  - 3-4 of 6 with DLT → consider stopping study
- 2-3 of 3 with DLT → consider stopping study

Dose Level 0
- 0 of 3 with DLT → move to Level 1
- 1 of 3 with DLT → 3 more at Level 0
  - 1 of 6 with DLT → move to Level 1
  - 2 of 6 with DLT → **expand Level 0 to 20 patients**
  - 3-4 of 6 with DLT → drop to Level -1
- 2-3 of 3 with DLT → drop to Level -1

Dose Level 1
- 0 of 3 with DLT → **expand Level 1 to 20 patients**
- 1 of 3 with DLT → 3 more at Level 1
  - 1-2 of 6 with DLT → **expand Level 1 to 20 patients**
  - 3-4 of 6 with DLT → **expand Level 0 to 20 patients**
- 2-3 of 3 with DLT → **expand Level 0 to 20 patients**

1.3 Schedule of Assessments

Tests and procedures	Pre-reg	≤14 days prior to start of therapy	Initial 4 weeks of progesterone therapy				Second 4 weeks of progesterone therapy	Subsequent maintenance progesterone therapy
			d1	d8	d15	d22	d29	Beginning of every 4 week interval to study end (up to 24 wks of therapy)[10]
Informed consent	X							
Path diagnosis	X							
H&P, KPS		X[4]			X[5]		X[5]	X[6]
Height (only initially), Weight		X			X[5]		X[5]	X[6]
Neuro assessment		X			X[5]		X[5]	X[6]
Adverse event assessment			X	X[5]	X[5]	X[5]	X[5]	X[6]
Medical History	X							
Concomitant medication	X	X	X	X[5]	X[5]	X[5]	X[5]	X[6]
Initial Consult	X[3]							
CBC w/diff		X					X[5]	X[6]
CMP[1]		X					X[5]	X[6]
Exploratory serum biomarkers		X					X[5]	
Pharmacokinetic assessment			X[8]	X[8]				
MRI w/ & w/o contrast[2]		X					X[5]	X[7]
Steroid/anti-Sz med documentation		X	X	X[5]	X[5]	X[5]	X[5]	X[6]
QOL assessments		X					X[5]	X[9]
Pregnancy test		X[11]						
Drug diary documentation			X[12]		X[12]		X[12]	X[12]

Note – AE assessments, concomitant medications and steroid/anti-Sz med documentation at d8 and d22 may be done by telephone, if the patient does not otherwise need to be seen in clinic.

[1] Comprehensive Metabolic Panel (CMP) - Sodium, potassium, bicarbonate, chloride, BUN, creatinine, calcium, glucose, total bilirubin, SGOT (AST), SGPT (ALT), alkaline phosphatase, albumin, total protein (Standard care). The frequency of CMP will be up to the treating physician's discretion.

[2] Standard diagnostic brain MRI w/ & w/o contrast.

[3] Initial consultation by either neuro-oncology or radiation oncology can be completed ≤ 21 days before initiation of therapy.

[4] May be satisfied by H&P at initial consultation if within 14 days of starting therapy.

[5] May be assessed ± 3 days.

[6] May be assessed ± 7 days. Final followup (including AE assessment) will be at 28 days after last drug dose.

[7] To be assessed after 8 weeks of therapy ± 1 week and then every 8 weeks ± 2 weeks, thereafter. Other MRIs can be done at discretion of treating physician, if needed.

[8] To be performed on day 1 (0, 30 minutes, 1, 2, 4, 6, 8 hrs from drug injection) as well as at day 8 prior to drug injections on those days only in patients getting PK evaluations. (May alternatively be done on any day after the 1st week during the initial 4 weeks with no need for day 8 trough draw if done later)

[9] To be assessed after 8 weeks of therapy ± 1 week and then 24 weeks ± 2 weeks, thereafter. Will be assessed for final time when patient comes off study (if it is prior to the 24 weeks evaluation and > 2 weeks from previous assessment).

[10] An end-of-study (EOS) visit (to include H&P, KPS, Weight, Neuro assessment, AE assessment, concomitant med, CBC, CMP) will be performed at 4 weeks ± 1 week after last drug dose. Beyond EOS visit, will continue to follow for local control, PFS and OS only at subsequent MRIs and follow-ups (per physician by normal clinical practice).

[11] For female subjects of childbearing potential (FCBP) only (see **Section 5.7** for definition of FCBP)

[12] A drug diary form will be given each time a supply of drug (2-week supply) is given to the patient and the previous drug diary will be collected at that time (see **Appendix 3** for sample form).

Pharmacokinetic Testing (Research)

Number of patients tested: The first three patients of a treatment dose level will undergo pharmacokinetic testing for plasma level of progesterone.

Timing of Assessments: Pharmacokinetic samples will be obtained on day 1 of therapy. Plasma samples will be obtained immediately prior to administration of drug and, subsequently, at 30 minutes, 1 hour, 2 hour, 4 hours, 6 hours, and 8 hours after drug injection. Additional sample will be obtained prior to the day 8 injection. (May alternatively be done on any day after the 1st week during the initial 4 weeks with no need for day 8 trough draw if done later)

Sample testing: After collection of plasma samples from three patients at one dose level (8 specimens/patient, 3 patients/dose level), batched samples will be sent to an internal Emory lab for testing of progesterone levels.

Quality-of-Life (QOL) Testing (Research): These questionnaires have been validated in the brain tumor population and used in other large, prospective studies for this patient population, providing a good potential comparison group for patients on this study. Subjects can opt out of this assessment if they so choose.

Timing of Assessments: Initial evaluations will be performed ≤ 14 days before starting natural progesterone. Subsequent evaluations will be at the following time points after initiation of study therapy (4 weeks ± 3 days, 8 weeks ± 1 week, 24 weeks ± 2 weeks) with one final off-study evaluation if it is prior to the 24 week evaluation and > 2 weeks from previous evaluation (this evaluation would be the visit when patient comes off study).

QOL Questionnaires: EORTC Quality of Life Questionnaire-Core 30/Brain Cancer Module-20 (EORTCQLQ30/BN20); M. D. Anderson Symptom Inventory Brain Tumor Module (MDASI-BT)

2. Objectives (and Endpoints)

Our main goal is to establish pharmacokinetics, safety/tolerability and efficacy of daily subcutaneous natural progesterone for the treatment of patients with recurrent glioblastoma. The specific objectives/endpoints of this study are listed below.

OBJECTIVES	ENDPOINTS
Primary	

OBJECTIVES	ENDPOINTS
• To determine that the pharmacokinetics of natural progesterone given to recurrent GBM patients by subcutaneous injection is consistent with previous determinations made using the aqueous formulation of progesterone (IBSA Institut Biochimique SA, Lugano, Switzerland) given subcutaneously. • To determine the safety of administering daily subcutaneous natural progesterone for the treatment of patients with recurrent GBMs. • To determine the ORR [defined as stable disease (SD) or better (PR or CR)] at 8 weeks in eligible patients with recurrent GBM treated with daily subcutaneous natural progesterone.	• Pharmacokinetic: Plasma progesterone levels at 0, 30 min, 1, 2, 4, 6, 8 hrs from 1st injection and at 8 prior to drug injection in 3 pts at each dose level. (May alternatively be done on any day after the 1st week during the initial 4 weeks with no need for day 8 trough draw if done later) • Safety: Adverse events, clinical assessments (eg. vital sign, physical, etc.), clinical laboratory test. • Efficacy: Overall response rate (ORR) per protocol volumetric definition at 8 weeks from initiation of progesterone.
Secondary	
• To determine and compare the progression-free survival of eligible patients with recurrent GBM compared with matched historical controls treated with a range of standard therapies. • To determine and compare the overall survival of eligible patients with recurrent GBM compared with matched historical controls treated with a range of standard therapies.	• Progression-free Survival (PFS) using protocol specified volumetric progression criteria. • Overall Survival (OS)
Tertiary/Exploratory	
• To determine whether progesterone receptor levels within the tumor correlates with response to daily subcutaneous natural progesterone. • To determine if other intrinsic tumor factors (mutations and genomic loss/gains, see **Section 5.7** for specific details) correlates with response to daily subcutaneous natural progesterone. • To determine if the absolute values or changes in the level of serum biomarkers (see **Section 5.7** for specific biomarkers) correlates with response to daily subcutaneous natural progesterone. • To determine the quality-of-life (QOL) by validated instruments of eligible patients with recurrent GBM treated with daily subcutaneous natural progesterone and assess whether this differs from historical controls.	• Levels of progesterone receptor expression by immunohistochemistry. • Specified intrinsic tumor factors (genetic/epigenetic changes, see **Section 5.7**). • Absolute levels/changes in specified serum biomarkers (see **Section 5.7**) before and 4 weeks after treatment with progesterone. • QOL assessment by the EORTC Quality of Life Questionnaire-Core 30/Brain Cancer Module-20 (EORTCQLQ30/ BN20) and M. D. Anderson Symptom Inventory Brain Tumor Module (MDASI-BT).

3. Background

Glioblastomas (GBMs) are aggressive primary brain tumors of astrocytic origin. Approximately ten thousand new cases are diagnosed each year in the U.S., making it the most common primary malignant brain tumor in adults. While radiation therapy (RT) has long been used in the treatment of GBMs and will delay their progression, it generally will not control these tumors long term. Incremental progress has been made in the management of GBMs, most recently with the addition of temozolomide (TMZ) chemotherapy to RT; however, outcomes remain poor, with a median survival of only 14-15 months [Stupp et al., 2005; Stupp et al., 2009]. Most recently, tumor treating fields were shown to further increase median overall survival in newly diagnosed GBM patients to approximately 20 months [Stupp et al., 2017]. Overall, nearly all patients will eventually fail primary therapy for the treatment of their GBM and will therefore require some form of salvage therapy.

As would be expected for a tumor that is generally not controlled by primary therapy, salvage therapies for recurrence of GBM have also been largely disappointing. Numerous strategies including repeat surgeries, cytotoxic chemotherapies, re-irradiation, targeted therapies, immunotherapies, tumor-treating fields, etc. have all been tried with very limited success. The survival of patients with recurrent GBM is extremely poor and even in the best setting (e.g. at 1st recurrence), median survival is generally still less than 1 year [Seystahl et al, 2016]. A number of factors contribute to the poor results with salvage therapy including the infiltrative nature of GBMs making complete surgical removal impossible, resistance to radiation especially in the setting of GBM that has recurred following previous irradiation, and presence of a blood-brain barrier (BBB) which excludes to varying extents potential systemically administered therapeutic agents. Clearly, new therapies are still needed for these aggressive brain tumors especially in the recurrent setting.

3.1 Study Rationale

Progesterone - A promising candidate for systemically administered therapy: An agent which has no demonstrable negative effects on healthy cells but kills cancer cells efficiently and selectively would be a significant step forward for GBM treatment. One such agent may be the neurosteroid progesterone. It is a natural hormone made by both males and females which influences functions of both the central and peripheral nervous systems [Guennoun et al., 2019; Stein, 2017]. As a natural hormone, progesterone is readily available, easy to administer, safe, and very inexpensive. It crosses the BBB rapidly and one of its key effects is to reduce the cerebral edema and inflammation that often accompany severe brain injuries from trauma, surgical excision of brain tissue, chemotherapy, or radiation [Adamson et al. 2009]. Progesterone has been shown to have a very high safety profile and limited side effects in clinical treatment for brain injury [Wright et al. 2007].

Is Progesterone Neuroprotective or Cytotoxic?

The dose matters (hormesis): Hormesis is a dose response phenomenon characterized by low-dose stimulation and high-dose inhibition, resulting in either a J-shaped or an inverted U-shaped dose response (Fig. 1). Progesterone shows a typical inverted U-shaped hormetic effect, as we have reported in GBM [Atif et al. 2015a; 2015b]. Several other drugs have also been reported to exert a hormetic effect, including some chemotherapeutic [Reynolds 2010; Bao et al. 2015] and neuroprotective drugs for stroke and trauma

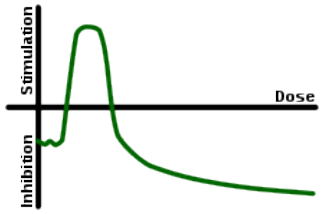

Fig. 1: Hormesis

[Calabrese 2008; Howard et al. 2017]. Therefore, it is of critical importance to select the right dose of a therapeutic agent.

High-Dose Progesterone is Anti-Tumorogenic: Why do we think progesterone could be a potential agent for GBM treatment? As a gestational hormone, progesterone plays a critical role in fetal growth, which must be well controlled for normal development. The outer ring of placenta cells are extremely aggressive, behaving somewhat like tumor cells as they invade the uterine wall and tap into the mother's blood vessels. Among the numerous factors that control cell cycle machinery to check abnormal growth, progesterone plays a pivotal role in meiosis and mitosis by regulating the activity of positive regulators (cyclins and CDKs) and inhibitors ($p21^{Cip1}$ and $p27^{Kip1}$) of the cell cycle through the progesterone receptor (PR) [Dressing and Lange 2009]. High natural progesterone levels during pregnancy (10x or more) are associated with a lower incidence of maternal breast cancer, and also appear to exert a long-term protective effect against breast cancer [Peck et al. 2002]. ***A substantial literature supports the anti-proliferative and apoptotic effects of progesterone on breast, endometrial, ovarian, colon and salivary gland tumors in vitro and in vivo*** **[Diep et al. 2013;** Bu et al. 1997; Formby and Wiley 1999; Horita et al. 2001; Medina et al. 2007; Altinoz et al. 2019**].** A recent study also suggests that high-dose progesterone prevents high-grade serous ovarian cancer *in vitro* (100 µM) and *in vivo* (5 mg/kg) [Wu et al. 2017].

Progesterone Exerts Anti-Tumor Effects in GBM: We performed and reported a number of *in vitro* and *in vivo* studies evaluating anti-tumor effects of high dose progesterone using different grade IV human GBM cell lines. Also, we tested safety of high dose progesterone in both *in vitro* and *in vivo* models. Our data strongly suggest that:

(1) Progesterone exerts selective cytotoxicity at high doses in GBM cells in vitro. We tested progesterone's anti-proliferative effects against a variety of GBM cell lines, and reported a significant anti-proliferative effect of high-dose progesterone with no cytotoxicity toward non-neoplastic cells such as primary neurons (non-dividing) and primary human dermal fibroblasts (dividing) at the same high doses [Atif et al. 2015a; Atif et al. 2015b].

(2) Progesterone outperforms TMZ in vitro. We tested and compared the efficacy of progesterone and TMZ in human GBM cell lines U87MG and U118MG. We reported that high dose progesterone outperforms TMZ, and when given in combination, enhances TMZ's cytotoxicity in GBM cells and reduces its toxicity in primary healthy cells [Atif et al. 2015b].

(3) High-dose progesterone exerts anti-metastatic effects on GBM. GBM is highly invasive and infiltrates to the adjacent tissue. We tested and compared both progesterone and TMZ, alone or in combination, for their effects on cell migration of a highly invasive U87MG cell line using wound-healing assay. We found that progesterone not only outperformed TMZ when tested alone, but also enhanced TMZ's anti-migratory effects in combination [Atif et al. 2015b].

(4) High-dose progesterone reduces drug resistance in GBM cells. The mechanism of action of TMZ is based on its capacity to methylate DNA, which causes cellular cytotoxicity by forming O6-methylguanine adducts. Unfortunately, GBM cells develop resistance to TMZ that is mediated by a DNA repair protein, O6-methylguanine-DNA-methyltransferase (MGMT), which removes TMZ-generated DNA adduct. Resistance to TMZ is a major obstacle to treating GBM patients. We found that high dose progesterone inhibits MGMT expression in U118MG cell line of human GBM suggesting its role in reducing drug resistance [Atif et al. 2015b].

(5) High-dose progesterone suppresses tumor growth and prolongs survival in an orthotopic model of GBM in nude mice. We tested progesterone's anti-tumor effects in an orthotopic GBM mouse model using a luciferase-stable U87MG cell line. After 7 days of cell inoculation, we first confirmed tumor occurrence with bioluminescent imaging (BLI) and then started vehicle (30% β-hydroxy cyclodextrin) or progesterone

treatment (8 and 100 mg/kg; with a daily, single, subcutaneous injection for 4 weeks). By day 28, all the animals in the vehicle group reached the maximum allowable tumor burden with neurological signs for euthanasia. We found that, compared to vehicle treatment, progesterone reduced tumor size at both 8 and 100 mg/kg doses but the 100 mg dose was more effective. Progesterone at both doses enhanced survival rate compared to vehicle-treated mice but 100 mg was more effective (~43% increase) [Atif et al. 2019].

(6) High-dose progesterone is well tolerated and exerts no toxicity in liver and kidney of nude mice. The high dose of progesterone (100 mg) was well tolerated by nude mice as measured by daily monitoring of their activity levels. No sign of toxicity was observed as evidenced by examining the histology of liver and kidney [Atif et al. 2019]. Tissue sections showed no evidence of acute, chronic, or granulomatous inflammation. There was no evidence of tissue injury, such as frank necrosis, edema, fibrosis, hemorrhage, congestion, or acute cellular toxicity. In the kidney, there was no acute tubular necrosis, and the liver showed no evidence of centrilobular necrosis. The tissue further showed no signs of enlargement, atrophy, or gross evidence of vascular congestion. All results indicate no toxicity associated with high-dose progesterone.

(7) High-dose progesterone inhibits proliferation, angiogenesis and induces apoptosis by inhibiting EGFR/PI3K/Akt/mTOR signaling in vivo. Our data from tumor tissue suggest an inhibitory effect of high-dose progesterone on GBM proliferation, angiogenesis, and induction of apoptosis [Atif et al. 2019]. The EGFR/PI3K/Akt/mTOR signaling pathway is known to be highly active in GBM patients. It plays a critical role in drug resistance by facilitating tumor proliferation and angiogenesis and inhibiting apoptosis even after chemo or radiotherapy [Wee and Wang 2017; Li et al. 2016; Padfield et al. 2015]. We found high expression levels of phospho-Akt and mTOR in the vehicle group, which supports our observations of increased proliferation and angiogenesis in that group. The progesterone-treated group showed significantly lower expression of Akt, phospho-Akt, mTOR and phospho-mTOR in tumor tissue compared to vehicle controls. This inhibitory effect of progesterone on PI3K/Akt/mTOR signaling correlates with the observed decreased levels in markers of proliferation and angiogenesis.

(8) Progesterone inhibits mitochondrial respiration and induces senescence in GBM cells. Preference for glycolysis over mitochondrial oxidation supports high anabolic activity of cancer cells, which results in uncontrolled proliferation, migration, invasion and metastasis. We have recently shown that high-dose progesterone inhibits glycolytic metabolism in three genetically different GBM cell lines and induces premature senescence in GBM cells *in vitro* [Atif et al. 2019]. As a direct measure of progesterone's effect on GBM cell metabolism, we showed a dose-dependent inhibitory effect of progesterone on ATP levels in three GBM cell lines [Atif et al. 2019].

(9) Progesterone improves the quality of life of tumor-bearing mice. We recorded spontaneous locomotor activity of tumor-bearing mice at different time points to evaluate the effect of the growing intracranial GBM tumor and the effects of progesterone treatment on behavioral outcomes associated with sickness behaviors [Atif et al. 2019]. We observed that with increasing intracranial GBM growth, mice in the vehicle group started to show functional decline compared to their non-tumor-bearing counterparts. At week 3, the vehicle-treated animals were found to be more restless or hyperactive, as evidenced by distance travelled and resting time tests. In contrast, progesterone-treated mice showed activity comparable to that of the non-tumor-bearing mice. At week 4, when the tumor size was larger, the vehicle group mice became very weak, lost body weight, and were less mobile. Interestingly, progesterone-treated mice fared much better and their activity level was similar to that of the non-tumor-bearing mice. We think that the growing tumor led to the behavioral sickness behaviors, probably because of increasing intracranial pressure, cerebral edema and chronic inflammation. It is worth noting here that progesterone has been shown to improve behavioral deficits in a number of brain injury models including stroke and traumatic brain injuries [Guennoun et al. 2019; Deutsch et al. 2013].

(10) Progesterone improves therapeutic cranial irradiation-induced neurocognitive deficits in mice. Despite improved therapeutic methods, CNS toxicity resulting from cancer treatment remains a major cause of post-treatment morbidity. More than half of adult patients with cranial irradiation for brain cancer develop neurobehavioral/cognitive deficits that severely impact quality of life. We examined the neuroprotective effects of progesterone against ionizing radiation (IR)-induced neurobehavioral/cognitive deficits in mice. We evaluated both hippocampus-dependent and -independent memory functions. Our data suggest that progesterone treatment improves IR-induced neurobehavioral/cognitive deficits by modulating inflammatory astrocyte activation, neuroinflammation and apoptosis in the brain. These findings could be important in the context of patients with brain tumors who undergo radiotherapy and eventually develop cognitive deficits [Yousuf et al. 2017].

High anti-tumor levels versus normal/physiological levels of progesterone: In our previous study (Atif et al. 2011), we measured progesterone (P4) bioavailability in mice serum 24 h post-P4 administration. P4 was administered as a single subcutaneous injection at 50 and 100 mg/kg body weight doses. Analysis of serum by radioimmunoassay (RIA) revealed very high levels of P4 in both the 50 and 100 mg/kg groups (Fig. 2). Average serum P4 levels were 14.91 ng/mL in mice given 50 mg/kg, whereas mice given 100 mg/kg showed 31.14 ng/mL P4. **The P4 level in vehicle group (no P4) was found to be 5.16 ng/mL.** Interestingly, P4 at both the high doses showed significant ($p < 0.001$) tumor reduction by ~50% after just 8 days of daily treatment compared to the vehicle group. **These findings suggest that in mice, serum P4 levels at 14.91 ng/mL or above exert anti-proliferative effects while normal/physiological serum P4 level (~5.16 ng/ml or below) were not effective in reducing tumor growth.**

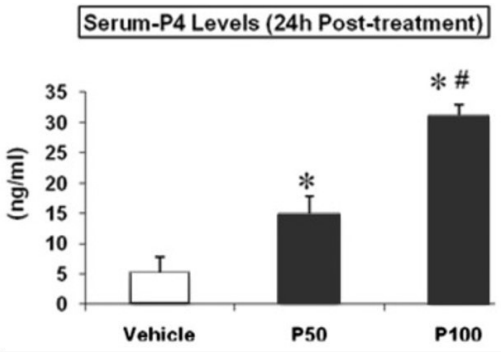

Fig 2. Serum P4 levels in mice serum by RIA. Data are expressed as means ± standard error of the mean (SEM) different groups (n = 12) from two independent experiments. Significant difference: *$p < 0.001$ compared with vehicle group; #$p < 0.001$ compared with P50 group, 50 mg P4 dose; and P100 group, P4 100 mg dose.

Based on our mice serum P4 and tumor volume data (Atif et al. 2011), we aim to achieve serum P4 levels higher than the normal physiological P4 levels in human. If we compare with normal physiological circumstances, luteal phase levels of P4 are 4 to 30 ng/mL, while follicular phase levels of P4 are 0.02 to 0.9 ng/mL, **menopausal levels are 0.03 to 0.3 ng/mL, and levels of progesterone in men are 0.12 to 0.3 ng/mL** (Josimovich, 2013; Sampson, 1981). Therefore, we expect to observe anti-proliferative effect of P4 at a dose where we could achieve serum levels higher than 0.3 ng/ml in men and menopausal women.

The pharmacokinetics data of the proposed test drug, Prolutex, reveal very high levels of serum P4 (Cmax) in human following a single subcutaneous injection. A single subcutaneous dose of 25 mg produces a Cmax = 57.8±13.6; 50 mg dose produces a Cmax = 103±24.5; and 100 mg dose produces a Cmax = 235±62.6 (Cometti, 2015) (see **Section 4.1**).

Now, if we compare the normal/physiological levels of P4 in human (~0.3 ng/ml) with the Cmax produced by a single 25 mg dose of Prolutex (~58 ng/ml), we observe a **~192 folds increase** in serum P4 levels. These high levels of P4 in human serum are also **~2.9 folds higher** compared to the mice serum levels. Taken together, we do not expect any proliferative effect of P4 at a dose of 25 mg in GBM patients given the very high serum P4 levels after P4 administration.

Summary: The above discussion provides significant pre-clinical evidence that natural progesterone has activity against GBM cells/tumors and that the anti-tumor levels used in pre-clinical models is achievable within patients. Based on the accumulating data, we feel that it is warranted to test progesterone for safety/tolerability and efficacy in patients with recurrent GBM.

3.2 Clinical Experience

Medical Uses of Progesterone

Progesterone has been in clinical use since 1934 and was ranked as 189th most prescribed medication in the United States in year 2016 with more than 3 million prescriptions (https://en.wikipedia.org/wiki/Progesterone_(medication)#Medical_uses). Progesterone is currently being used in hormone therapy, pregnancy support, fertility support, birth control and gynecological disorders. In hormone replacement therapy, progesterone is used specifically to provide endometrial protection against unopposed estrogen-induced endometrial hyperplasia and cancer in women with intact uteruses [Archer et al. 2019; Kuhl 2005]. The current literature on the role of progesterone in health and disease is now immense, so much is known about its safety and pharmacologic parameters in a wide variety of disorders, including those of the central nervous system. For example, a quick search on just progesterone and inflammation on PubMed, reveals about 1500 papers. For research using progesterone in brain injury the number is 470. Searching for progesterone use on *Clinicaltrials.gov* showed that there are over 1450 trials listed. Of the first 450 trials listed, most address women's health issues such as IVF, prevention of premature birth, menstrual cramps, and infertility among others. However, other trials have tested progesterone for nicotine dependence, tobacco use disorder, endometrial polyps, reduce cannabis dependence, cocaine abuse, acute hemorrhagic stroke, endometrial cancer treatment, polycystic ovary syndrome, night sweats, concussion, alcohol dependence, post-traumatic stress disorder, congenital heart disease, embryo preservation, epilepsy, preeclampsia, bulimia nervosa, recurrent or persistence endometrial carcinoma, postmenopausal sleep disorders, postpartum depression,, and bipolar disorder. There is unequivocal evidence that progesterone is safe as demonstrated by its current clinical uses and the fact that FDA has approved a number of clinical trials with progesterone is highly vulnerable populations with a variety of very dangerous as often deadly illnesses.

Route of Administration for Progesterone

Based on the above discussion, progesterone clearly has a range of medicinal effects including, in particular, anti-GBM activity in different disease models. To test whether progesterone is effective at treating glioblastomas, we need to find a means of dosing patients to achieve high systemic levels using a convenient and easy route of administration. Progesterone has been given in a number of ways including orally, through mucosal surface absorption (e.g. vaginal or rectal administration) or via injection (eg. intramuscular or subcutaneously administration). While oral administration is very convenient and an FDA-approved oral capsule form of progesterone is available (eg. Prometrium), this drug has a relatively low oral bioavailability with a typical 200 mg dosing producing a C_{max} in the 5-10 ng/mL range. Due to first-pass hepatic metabolism, very high levels of metabolites including allopregnanolone and pregnanolone occur and can circulate as neurosteroids with strong potentiation of $GABA_A$ receptors leading to the commonly reported side effects of dizziness, drowsiness, sedation, somnolence and fatigue. This factor really limits how high a dose of oral progesterone can be used. In regards to mucosal absorption approaches, both vaginal and rectal suppositories have been used. Tablet and capsule forms of progesterone for vaginal administration is available in the United States (US) but the 100 mg dose still only produces a C_{max} of approximately 10 ng/mL and would only be an option for female patients. While rectal suppositories can be used for either sex, C_{max} is generally lower (approximately 80% of what is achievable with comparable dose vaginal administration) and there is still some level of first-pass hepatic metabolism. In addition, no formulation has been approved by the FDA for use in the US via this route of administration. Finally, in regards to injection, both intramuscular (IM) and subcutaneous (SC) administration have been examined. Since progesterone is lipid-soluble, progesterone for IM injection have been primarily administered within an oil-based solution. While the IM route can achieve very high plasma drug levels and even has somewhat of a depot effect which could

permit less frequent dosing (up to 3 days between doses), it is often associated with moderate-to-severe injection site reaction and patients would typically not be able to self-administer this formulation. On the other hand, SC injection is now possible through an aqueous formulation developed by IBSA Institut Biochimique SA (Lugano, Switzerland). This formulation (marketed as Prolutex™ in Europe) dissolves the lipophilic natural progesterone as an aqueous solution containing β-cyclodextrin. This aqueous formulation of progesterone can be conveniently self-administered by patients and produces high systemic levels on the order of 20-40 fold higher than what is achievable with oral administration. The pharmacokinetics of aqueous SC progesterone is presented below (**Section 5.1**). Given these advantages, we have opted to use this formulation for SC injection in this current study.

4. Study Intervention/Investigational Agent

4.1 Description

Natural Progesterone

Chemical Name: pregn-4-ene-3, 20-dione (molecular weight 314.47, molecular formula $C_{21}H_{30}O_2$)

Other Names: Progesterone

Mechanism of Action: Progesterone is a progestogen, and an agonist of the nuclear progesterone receptors (PRs), the PR-A, PR-B, and PR-C [Kuhl, 2005]. In one study, progesterone showed EC_{50} values of 7.7 nM for the human PR-A and 8.0 nM for the human PR-B [Attardi et al. 2004]. In addition to the PRs, progesterone is an agonist of the membrane progesterone receptors (mPRs), including the mPRα, mPRβ, mPRγ, mPRδ, and mPRϵ [Guennoun 2020; Ryu et al. 2017]. It is also a potent anti-mineralocorticoid (antagonist of the mineralocorticoid receptor (MR)) [Rupprecht et al. 1993; Elger et al. 2003], as well as a very weak glucocorticoid (agonist of the glucocorticoid receptor) [Attardi et al. 2007; Lei et al. 2012].

Pharmacokinetics:

Graph/table of plasma progesterone levels after subcutaneous injection[a]

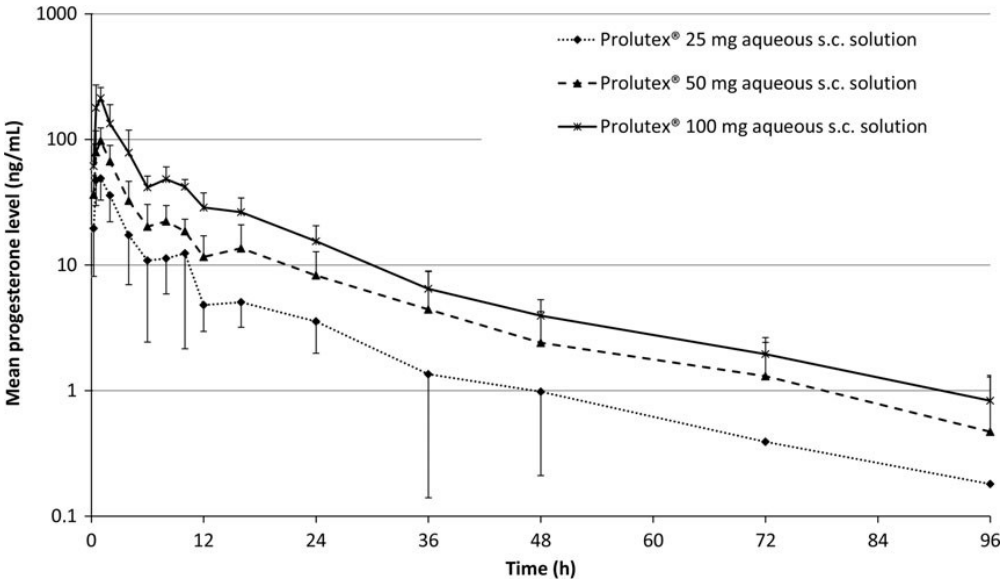

Table 2. Main progesterone baseline-corrected pharmacokinetic parameters (mean ± sd) calculated after subcutaneous administration of a Prolutex® single dose of 25, 50 and 100 mg. *n* = 12.

Pharmacokinetic parameter	25 mg	50 mg	100 mg
C_{max} (ng/mL)	57.8 ± 13.6	103 ± 24.5	235 ± 62.6
T_{max} (h)	0.92 ± 0.42	0.92 ± 0.42	0.92 ± 0.42
AUC_{0-t} (ng/mL/h)	338 ± 91.6	729 ± 228	1466 ± 213
$AUC_{0-\infty}$ (ng/mL/h)	349 ± 91.1	746 ± 250	1490 ± 213
t½ (h)	13.1 ± 7.1	17.2 ± 5.1	17.6 ± 5.8

AUC_{0-t}, area under the curve from time 0 to the last observed concentration time t; $AUC_{0-\infty}$, area under the curve extrapolated to infinity; C_{max}, maximum serum concentration; T_{max}, serum peak concentration time, t½, half-life.

[a] [Cometti 2015]

Metabolism and Elimination: Progesterone is metabolized primarily by the liver largely to pregnanediols and pregnanolones. Pregnanediols and pregnanolones are conjugated in the liver to glucuronide and sulfate metabolites. Progesterone metabolites which are excreted in the bile may be deconjugated and may be further metabolized in the intestine via reduction, dehydroxylation, and epimerization.

The glucuronide and sulfate conjugates of pregnanediol and pregnanolone are excreted in the bile and urine. Progesterone metabolites are eliminated mainly by the kidneys. Progesterone metabolites which are excreted in the bile may undergo enterohepatic recycling or may be excreted in the feces.

The elimination half-life of the subcutaneous progesterone formulation (aq. for SC injection) is 13 to 18 hours. Pharmacokinetic assessments of this formulation will be determined for a limited number of recurrent GBM patients on this study to assure similar pharmacokinetic behavior compared with previous assessments of subcutaneous progesterone.

4.2 Drug/Device Handling

Drug Source: Subcutaneous progesterone; IBSA Institut Biochimique SA.

Formulation: Progesterone 25 mg/vial aqueous injection suspension.

Route of Administration: Subcutaneous (alternate over different sites).

Site of Storage: Winship Investigational Drug Service (IDS).

Storage and Stability: Store at 20°C to 25°C (68° to 77°F), and excursions of 15°C-30°C (59°-86°F) are permitted (see USP Controlled Room Temperature. Do not freeze nor refrigerate. The product should be protected from exposure to light.

Drug handling: Stored drug will be handled per the SOP of the Winship IDS. Once a dose level has been determined for a particular patient, the Winship IDS will prepare enough dose to allow dispensing of a two-week supply of drug for the subject. Instructions will be given to the patient or their designee/caretaker regarding the handling procedure and method of administration (instructed on daily subcutaneous administration by a licensed individual per Winship SOP 6.2) of the progesterone. The patient will need to return every two weeks to pick up their next medication supply.

IND Holder: Hui-Kuo G. Shu, MD, PhD (as the Sponsor-Investigator).

4.3 Accountability

The aqueous progesterone for injection (study drug) provided for this study will be used only as directed in the study protocol. The study drug will be provided by the company (IBSA Institut Biochimique SA, Lugano, Switzerland). Winship IDS personnel will account for all study drug. Drug accountability should be performed until the patient stops study treatment completely.

Study drug supplies must be kept in an appropriate, secure locked area and stored in accordance with the conditions specified on the labels. The Investigator, pharmacist, or designee must maintain an accurate record of dispensing the study drug in a Drug Accountability Log.

The Drug Accountability Log may record specifics to study drug dispensation such as:

• Records of product delivery, inventory, temperature monitoring, destruction, and return.

• Dosages prepared, time prepared, doses dispensed.

• Doses and/or vials destroyed.

• The Drug Accountability Log may be reviewed by the monitor during site visits and at the completion of the study.

Drug accountability may be noted by the internal monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

The study drug supply will be disposed of per Winship's Investigational Drug Service (IDS) SOP.

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver (collection of drug diary) will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit.

Dose level for individual patients will be verified by two individuals authorized on study: the investigator or sub-investigator ordering the study drug and another licensed staff member, such as, Pharmacist (Pharm. D.), physician-investigator (M.D.), CRN, or Advanced Practice Providers (APP), and 2 weeks of drug at a time will be dispensed for patient to self-administer. The patient will be requested to maintain a medication diary of each dose of medication. The medication diary (**see Appendix 3**) will be returned to clinic staff every two weeks when patient returns for their next supply.

Dose changes and interruptions of study drug must be specifically documented in the patient source documents and eCRF.

5. Procedures Involved

5.1 Study Design

This clinical trial is a Phase 1 pilot study assessing the pharmacokinetics, safety/tolerability, and antitumor efficacy of aqueous injectable progesterone for the treatment of recurrent GBM (see Schema in **Section 1.2**).

Dose-Finding: Part 1 comprises the initial dose-finding phase of the study where 3+3 patients will potentially be enrolled and treated at each dose level (levels -1 to 1) to find the highest dose that is both safe and tolerable for eligible patients with GBM at 1st to 3rd recurrence. Subjects will receive aqueous progesterone for injection subcutaneously on a daily basis at the currently assessed dose level for up to 24 weeks unless the patient is discontinued prior to that time for one of the reasons specified below.

Cohort Expansion: Part 2 comprises the expansion phase of the study where a total of 20 patients will be treated at the highest dose identified to be safe and tolerable during Part 1 of the study. Subjects will receive aqueous progesterone for injection subcutaneously on a daily basis at the dose level determined in Part 1 of the study for up to 24 weeks unless the patient is discontinued prior to that time for one of the reasons specified below.

The study is divided into a Screening period, Treatment period, and End of Treatment (EOT) period.

During the Screening period patients will provide written informed consent to participate in the study before completing any protocol-specified procedures or evaluations not considered to be part of the patient's standard care. Procedures that were performed for standard of care prior to signing informed consent may be used for screening purposes (e.g., full physical exam) as long as the procedures were completed within the **14-day screening period** prior to initiation of progesterone therapy. After signing the ICF, patients will be evaluated for entry criteria during the screening period within 14 days before administration of study drug(s). Rescreening after screen failure will be allowed.

For the Treatment period, patients will be treated with progesterone for up to 24 weeks unless there is unacceptable toxicity, death, disease progression per protocol-specified criteria, Investigator's decision to discontinue treatment, the patient withdraws consent, is lost to follow-up, or Institution decides to terminate the trial.

Patients with progressive disease (PD) per protocol-specified criteria but with otherwise stable or improved performance and clinical status may continue to be treated in the event of a perceived benefit per Investigator. Patients who are tolerating the drug with stable disease (SD) or better after 24 weeks of therapy may be considered for compassionate use continuation on a case-by-case basis after discussions between the patient, treating physician and the study supporter (IBSA Institut Biochimique SA, Lugano, Switzerland). It is at the discretion of the Investigator to continue treating patients in this circumstance as long as IBSA agrees to continue to provide drug until unacceptable toxicity, disease progression or patient withdrawal. Followup evaluations under these circumstances will be considered standard-of-care at the discretion of the patient's treating physician.

The EOT period would last for 4 weeks after drug discontinuation at which point the end-of-study (EOS) visit would occur where final Adverse Event (AE) documentation and other study-required assessments are performed. Further assessment of progression or death for determination of PFS and OS will be based on review of records obtained after this point on a retrospective basis where additional treatments and followup intervals will be at the discretion of the patient's treating physician.

5.2 Dosing and Administration

Formulation: An aqueous formulation of natural progesterone complexed with 2-hydroxypropyl-β-cyclodextrin (Subcutaneous progesterone; IBSA Institut Biochimique SA, Lugano, Switzerland) will be used. An IND for this formulation will be cleared by the FDA and cross-referenced to support the present study.

Route of administration: Each dose (25-75 mg) will be given daily by subcutaneous injection using a tuberculin syringe with sterile technique. The site of injection will rotate along different sites (standard locations including abdomen, thigh) based on patient preference with at least 1 day break between reinjection of a particular site. Each injection will consist of 25-50 mg of drug in 1-2 ml with multiple injections to be used if higher doses of drug are called for per study.

Timing of administration: Drug will be injected subcutaneously at about same time in the AM ± 3 hours each day.

Pharmacokinetic assessment (only 1st 3 patients at each dose cohort): Will only be done on the first three patients at each dose level cohort. Assessment time points will be start on day 1 of treatment. Blood draws will be performed immediately prior to drug administration (by subcutaneous injection). Subsequent blood samples will be obtained at 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours and 8 hours following progesterone injection. One additional time point will be performed on day 8 just prior to drug injection on those days.

Dose Finding Phase (Part 1):
Patients will be enrolled sequentially and will follow a 3+3 design. The dose levels that will be potentially used are on the following table:

Dose Level	Dose of aqueous natural progesterone for injection (mg)
Level -1	25
Level 0	50
Level 1	75

Dosing will start at Dose Level 0 and will escalate or de-escalate according to the following rules:

Dose Level -1
- 0 of 3 with DLT → **expand Level -1 to 20 patients**
- 1 of 3 with DLT → 3 more at Level -1
  - 1-2 of 6 with DLT → **expand Level -1 to 20 patients**
  - 3-4 of 6 with DLT → consider stopping study
- 2-3 of 3 with DLT → consider stopping study

Dose Level 0
- 0 of 3 with DLT → move to Level 1
- 1 of 3 with DLT → 3 more at Level 0
  - 1 of 6 with DLT → move to Level 1
  - 2 of 6 with DLT → **expand Level 0 to 20 patients**

3-4 of 6 with DLT → drop to Level -1
2-3 of 3 with DLT → drop to Level -1

Dose Level 1
0 of 3 with DLT → **expand Level 1 to 20 patients**
1 of 3 with DLT → 3 more at Level 1
1-2 of 6 with DLT → **expand Level 1 to 20 patients**
3-4 of 6 with DLT → **expand Level 0 to 20 patients**
2-3 of 3 with DLT → **expand Level 0 to 20 patients**

During the dose finding phase of the study, a treatment will be considered safe/tolerable if no DLT defined as ≥ grade 3 toxicity during the first 4 weeks drug therapy not clearly due to the underlying disease or extraneous causes with exceptions as noted in **Section 5.3**. After treatment initiation of up to 6 patients at a dose level and continuation for a minimum of 4 weeks with AE assessment, enrollment to the next (higher or lower) dose level as determined by the rules will only start after data is presented to the Winship Data Safety Monitoring Committee (DSMC) and final approval is obtained for starting the next dose level.

Dose escalations will be reviewed by the Winship Data Safety Monitoring Committee (DSMC) (per Winship SOP 7.9 Dose Escalation Determinations for Sponsor-Investigator or Investigator Initiated Studies). The PI or designee will provide an update on all relevant safety data of patients entered to a dose level to the DSMC when dose escalation is planned. Upon obtaining approval from the DSMC, dose escalation can proceed.

Dose Expansion Phase (Part 2):
The purpose of cohort expansion is to gather additional safety and tolerability information, and evaluate the efficacy of aqueous natural progesterone for injection at the dose determined by the Dose Finding Phase of the study.

The PI or designee must provide the DSMC a report outlining the overall enrollment and path to decision for the escalation dose(s) selected.

Continuous evaluation of toxicity events in the cohort expansion will be performed throughout enrollment in the expansion cohort. If, at any time, the aggregate rate of treatment-related toxicities meeting DLT criteria exceeds 33% across all subjects treated in the expansion cohort, the findings will be discussed and further enrollment may be interrupted. Depending on the nature and grade of the toxicity and after assessing the risk:benefit ratio, a new dose(s) for all cohorts may be initiated at a previously tested lower dose level, or at a dose level intermediate to previously tested lower dose levels.

In addition to continuous evaluation of toxicity, there will be one interim efficacy evaluation for futility. It is known that random ineffective therapies for recurrent GBM may still produce a response rate of 10%. Therefore, the overall response rate (ORR) for first 10 patients (1/2 of planned expansion cohort size) that undergo treatment with the subcutaneous progesterone at the final dose from the dose finding phase of the

study will be determined. If the ORR at the 8 week assessment time point is 20% (2 of 10) or greater, then the study will be declared potentially non-futile and enrollment of the full expansion cohort (N=20) will proceed. If the ORR at this time point is 10% (1 of 10) or less, then the study will be declared futile and further enrollment will be aborted. If the study is declared futile at this interim analysis, new enrollment will be discontinued but any patients that is still on therapy at that time will be allowed to continue therapy as long as they meet criteria to continue therapy as defined in Section 8.1 (e.g. continue to not have protocol-specified progressive disease).

5.3 Definition of Dose-Limiting Toxicity

The safety of this approach will be confirmed by assessing toxicity potentially attributable to the daily progesterone treatment. National Cancer Institute Common Terminology Criteria for Adverse events version 5.0 (NCI CTCAE v. 5.0) will be used for all grading. A dose limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value assessed as grade 3 or greater that is not clearly due to the underlying disease or extraneous causes with the following exceptions:

- Grade 3 nausea/vomiting or diarrhea for less than 72 hours with adequate antiemetic and other supportive care.
- Grade 3 fatigue for greater than 1 week.
- Grade 3 or higher electrolyte abnormality that lasts up to 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions.
- Grade 3 or higher amylase or lipase that is not associated with symptoms or clinical manifestations of pancreatitis.
- Grade 3 neutropenia.
- Grade 3 thrombocytopenia without clinically significant bleeding.

For the Dose Finding Phase of the study, the dose will be deemed tolerable if no DLTs occurs within the first 4 weeks of progesterone treatment. Prior to enrolling patients into a higher dose level, CTCAE grade ≥ 2 adverse events will be reviewed for all patients at the current dose level.

Management and dose modifications associated with adverse events are outlined in **Section 5.4**.

Dose escalation will proceed to different dose levels according to the scheme presented earlier (**Section 5.2**).

5.4 Dose Modification

Progesterone will be withheld for any instance of a CTCAE v5.0 grade 3 or greater toxicity (except for grade 3 neutropenia or grade 3 thrombocytopenia without clinically significant bleeding). Drug may be resumed, at the discretion of the treating physician, if the toxicity has reduced to the grade 0-1 level within 14 days. Treatment will be discontinued if toxicity persists beyond 14 days. For toxicity not clearly due to the underlying disease or extraneous causes, 50% dose reduction of original dose will be used when resuming treatment after sufficient recovery of toxicity as defined above. If toxicity is clearly due to the underlying disease or extraneous causes, no dose reduction is required after sufficient recovery of toxicity as defined above. Treatment will also discontinue if there is development of a DLT after one dose reduction.

Progesterone will be discontinued if patient develops any specific contraindication for use of progesterone (e.g. thromboembolic event). The treating physician can also stop progesterone if he/she feels that doing so would be in the best interest of the patient.

5.5 Concomitant medication

Medications specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. These would include anti-coagulation therapy (e.g. Lovenox, warfarin, etc.), estrogen/progesterone therapy (including hormonal contraceptives) and other anti-GBM agents (including investigational ones). If patient is on avastin at the time of enrollment on the study, he/she will be allowed to remain on this to prevent rebound and potential difficulty interpreting results. If there is a clinical indication for one of these or other medications specifically prohibited during the trial, discontinuation from trial therapy may be required.

5.6 Study Procedures

Before initiating progesterone therapy, throughout the course of progesterone therapy, and following progesterone discontinuation, various clinical and diagnostic evaluations are outlined. The purpose of obtaining these detailed measurements is to ensure adequate **safety and tolerability assessments** as well as **efficacy assessments**. Clinical evaluations and laboratory/radiographic studies may be repeated more frequently, if clinically indicated. The Schedules of Assessments during the screening, treatment and post-treatment phases of study are summarized in **Section 1.3**.

Screening Phase

Screening procedures will be performed up to 14 days prior to initiation of progesterone therapy unless otherwise specified. All subjects must first read, understand, and sign the IRB-approved ICF before any study-specific screening procedures are performed. After signing the ICF, completing all screening procedures, and being deemed eligible for entry, subjects will be enrolled in the study. Procedures that are performed prior to the signing of the ICF and are considered standard of care may be used as screening assessments if they fall within the screening window.

The following procedures will be performed during the **Screening Phase**:

- Obtaining informed consent
- Review of eligibility criteria (including documentation of pathologic diagnosis of GBM)
- Medical history and demographics
- Complete physical exam (including neurologic assessment)
- Determining score on Karnofsky Performance Scale (KPS, **Appendix 1**)
- Vitals signs, weight and height
- Review of concomitant medications (including steroid and anti-seizure med documentation)
- MRI brain w/ and w/o contrast (show at least 1 cm^3 of progressing enhancing tumor)
- QOL assessments
- Serum sample for exploratory biomarkers
- Clinical laboratory tests for:
    - CBC with differential
    - Complete metabolic panel (CMP)
    - Serum or urine pregnancy test (for female subjects of childbearing potential (FCBP) only)

Treatment Phase

Patients will receive subcutaneous natural progesterone at the dose called for on study on daily basis for up to 24 weeks during the **Treatment Phase**. The following procedures are to be conducted during the **Treatment Phase** of the study while the patient is receiving progesterone therapy.

- Brief medical history, symptom-directed physical exam including KPS and neurologic assessment (on day 15, on day 29, every 4 weeks thereafter). Can be performed at ± 3 days during first 8 weeks and ± 7 days thereafter.
- Vitals signs, weight (on day 15, on day 29, every 4 weeks thereafter). Can be performed at ± 3 days during first 8 weeks and ± 7 days thereafter.
- Review of concomitant medications (including steroid and anti-seizure med documentation, every week during 1st 4 weeks, every 4 weeks thereafter). Can be performed at ± 3 days during first 8 weeks and ± 7 days thereafter.
- Drug diary documentation by patient (to be collected every two weeks when patient return to get new supply of medication).
- MRI brain w/ and w/o contrast (after 4 weeks, after 8 weeks, every 8 weeks thereafter). Can be performed at ± 1 week at the after 4 weeks MRI and ± 2 weeks thereafter.
- Adverse event (AE) assessment (every week during 1st 4 weeks, every 4 weeks thereafter). Can be performed at ± 3 days during first 8 weeks and ± 7 days thereafter.
- QOL assessment after 4 weeks ± 3 days, after 8 weeks ± 1 week, after 24 week ± 2 weeks (assess for final time if patient comes off study before 24 weeks and it is > 2 weeks from previous assessment).
- Serum sample for exploratory biomarkers after 4 weeks ± 3 days.
- Pharmacokinetic assessment on day 1 (0, 30 minutes, 1, 2, 4, 6, 8 hrs from drug injection) as well as at day 8 prior to drug injections (only in first 3 patients at each dose level). (May alternatively be done on any day after the 1st week during the initial 4 weeks with no need for day 8 trough draw if done later)
- Clinical laboratory tests for:
    - CBC with differential
    - CMP

Post-Treatment Phase

The **Post-Treatment Phase** is the period after progesterone is stopped to the end-of-study (EOS) visit. The EOS visit will be scheduled 28 days after discontinuation of progesterone (window for visit can be up to 2 weeks beyond 28 days).

The following will be performed at the EOS visit:

- Brief medical history, physical exam including KPS and neurologic assessment.
- Vitals signs, weight.
- Review of concomitant medications (including steroid and anti-seizure med documentation).
- AE assessment.
- Clinical laboratory tests for CBC with differential and CMP.

While patients will not be further followed for official study visits after the EOS visit, further data for PFS and OS endpoints may be obtained based on chart review of future standard-of-care visits with the subject's treating physician(s).

5.7 Description of Study Procedures

Medical history

Findings from medical history (obtained at screening) and physical examination shall be given a baseline grade according to the procedure for AEs. Increases in severity of pre-existing conditions during the study will be considered AEs, with resolution occurring when the grade returns to the pre-study grade or below.

Physical examination

Physical examinations should be conducted according to the Schedules of Assessments. Full physical examinations should be conducted at screening/baseline and the EOS visit (evaluate all major organ systems, including the following categories: general, head, eyes, ears, mouth/throat, neck, heart, lungs, abdomen, lymph nodes, joints, extremities, integumentary, neurologic, and psychiatric). Other examinations may be focused, at the discretion of the Investigator, to identify changes from baseline or evaluate changes based on the patient's clinical symptoms. Weight is to be recorded at each visit, height at screening/baseline visit only.

Neurological assessment

Will be assessed with timing according to the Schedules of Assessments. Although not used for determining response, it is useful to evaluate improvement in the neurologic exam, as compared with the baseline assessment, that should coincide with objective measurement of tumor size.

NEURO EXAM STATUS (compared to pre-treatment exam)	
Better	Must be on stable or decreasing dose of steroids
Same	Failure to qualify for better or worse
Worse	Include patients requiring increasing steroid doses to remain stable

Performance status assessment

Patients will be graded with timing according to the Schedules of Assessments on the Karnofsky Performance Scale (**Appendix 1**).

Vital signs

Vital signs (blood pressure [BP], pulse, temperature, and respiration rate) will be evaluated according to the Schedules of Assessments. Body weight is also recorded along with vital signs.

Clinical laboratory tests

The following clinical laboratory tests will be performed (see Schedules of Assessments):

- CBC with differential
  - Includes hemoglobin/hematocrit, white blood cells with automated differential, platelets
- Complete metabolic panel (CMP)
  - Includes sodium, potassium, bicarbonate, chloride, BUN, creatinine, calcium, glucose, total bilirubin, SGOT (AST), SGPT (ALT), alkaline phosphatase, albumin, total protein
- Pregnancy test (female subjects of childbearing potential (FCBP) only)
  - Criteria for those not considered FCBP
    - Age ≥ 55 years and one year or more of amenorrhea
    - Age < 55 years and one year or more of amenorrhea, with estradiol < 20 pg/ml
    - Age < 55 with prior hysterectomy but intact ovaries, with estradiol < 20 pg/ml
    - Prior bilateral oophorectomy

Toxicity (Adverse Event) assessment

Toxicities will be scored according to CTCAE v5.0. Evaluations for toxicity will be performed weekly during the 1st 4 weeks of progesterone therapy followed by every 4 weeks thereafter (through a total of up to 24 weeks drug therapy). Final assessment (EOS visit) will be 4 weeks after last drug dose.

MRI brain with and without contrast

Diagnostic brain MRI scans with and without contrast will be utilized to assess for response with timing according to the Schedules of Assessments. DSC perfusion imaging will also be obtained, if possible, but is not required. Volumetric assessment of progressive measurable contrast-enhancing disease (≥ 1 cm^3) will be performed at baseline. If there is no measurable disease at trial baseline scan (e.g. gross resection of all recurrent enhancing disease), patient is still eligible for study but will be assessed for progression based on criteria for non-evaluable disease (< 1 cm^3 of recurrent enhancing disease).

Imaging response criteria is defined below:

Measurable Disease: Measurable lesions are those with clearly defined margins by contrast-enhanced MRI scan that is at least 1 cm^3 in volume. All measurable lesions will be considered together. Clear enhancing lesions representing progressive tumor pre-treatment that is less than 1 cm^3 in volume will be considered non-evaluable disease.

Objective Status, To Be Recorded at Each Evaluation: Unless progression is observed, objective status can only be determined when ALL measurable sites and lesions are assessed.

Response Definitions:

- **Complete Response (CR):** Complete disappearance of all measurable disease in contrast-enhancing MRI. No new lesions. No evidence of non-evaluable disease. All measurable lesions and sites must be assessed using the same techniques as baseline. Patients must be on no steroids. If there is no enhancing disease present at baseline, then this criteria will not apply and the case will not be considered in the N when evaluating for % of patient achieving CR.
- **Partial Response (PR):** (Measurable disease only) Greater than or equal to 65% decrease under baseline in total tumor volume of all measurable lesions. No progression of non-evaluable disease (defined as progression to at least 1.5 cm^3 in volume). No new lesions. All measurable lesions and sites must be assessed using the same techniques as baseline. If there is only non-evaluable disease or no enhancing disease present at baseline, then this criteria will not apply and the case will not be considered in the N when evaluating for % of patient achieving PR.
- **Stable Disease (SD):** Does not qualify for CR, PR, or progression. The designation of SD requires a minimum of 8 weeks duration (2 assessment of stable disease from baseline at least 4 weeks apart). All measurable sites must be assessed using the same techniques as baseline. The steroid dose at the time of the scan evaluation should be no greater than the maximum dose used in the first 8 weeks from initiation of therapy.
- **Progressive Disease (PD):** 40% increase in the tumor volume of all measurable lesions over previous exam (over baseline if no decrease) using the same techniques as baseline, OR clear progression of non-evaluable disease (defined as growth to at least 1.5 cm^3 in volume), OR clear appearance of any new measurable lesion/site, OR clear clinical worsening or failure to return for evaluation due to death or deteriorating condition (unless clearly unrelated to this cancer).

Best Response: This will be calculated from the sequence of objective statuses. For patients with all disease sites assessed every evaluation period, the best response will be defined as the best objective status as measured according to the above criteria.

Pharmacokinetic Testing (Research)

Number of patients tested: The first three patients of a treatment dose level will be undergo pharmacokinetic testing for plasma level of progesterone.

Timing of Assessments: Pharmacokinetic samples will be obtained on day 1 of therapy. Plasma samples will

be obtained immediately prior to administration of drug and, subsequently, at 30 minutes, 1 hour, 2 hour, 4 hours, 6 hours, and 8 hours after drug injection. Additional sample will be obtained prior to the day 8 injection. (May alternatively be done on any day after the 1st week during the initial 4 weeks with no need for day 8 trough draw if done later)

Sample testing: After collection of plasma samples from three patients at one dose level (8 specimens/patient, 3 patients/dose level), batched samples will be sent to an internal Emory lab for testing of progesterone levels.

Quality-of-Life (QOL) Testing (Research)

These questionnaires have been validated in the brain tumor population and used in other large, prospective studies for this patient population, providing a good potential comparison group for patients on this study. Subjects can opt out of this assessment if they so choose.

Timing of Assessments: Initial evaluations will be performed ≤ 14 days before starting natural progesterone. Subsequent evaluations will be at the following time points after initiation of study therapy (4 weeks ± 3 days, 8 weeks ± 1 week, 24 weeks ± 2 weeks) with one final off-study evaluation if it is prior to the 24 week evaluation and > 2 weeks from previous evaluation (this evaluation would be the visit when patient comes off study).

QOL Questionnaires: EORTC Quality of Life Questionnaire-Core 30/Brain Cancer Module-20 (EORTCQLQ30/BN20); M. D. Anderson Symptom Inventory Brain Tumor Module (MDASI-BT) (**Appendix 2**)

Potential intrinsic tumor biomarkers (Research)

In our pre-clinical studies, progesterone treatment was shown to exert anti-tumor effects on glioblastoma via different growth/survival pathways involved in proliferation, vascularization/angiogenesis, glycolytic/oxidative metabolism, and apoptosis.

To evaluate these factors within the tumor, the glioblastoma tumor specimen from the time of initial diagnosis will be assessed for the following factors (performed either as part of the original neuropathologic assessment or from subsequent assessment of the original tissue block/slides). These factors will be correlated with outcomes of patients on study to determine if there are detectable associations with response to progesterone.

- **Progesterone receptor (PR-A and PR-B) –** To be determined by immunohistochemistry of glioblastoma tumor from original surgery with expression level reported on a scale of 0-4 [Atif et al. 2011].
- **MGMT methylation –** This will be determined by methylation-specific PCR with results reported as positive, negative or borderline. All patients originally diagnosed at Emory has this test performed as part of the routine neuropathologic assessment. Will plan to use results from original pathology report unless it was not performed in which case the original tumor tissue block will be obtained for this testing [Atif et al. 2019].
- **Mutations in the following genes (p53, EGFR, PTEN, AKT, IDH1, IDH2) –** Sequence variation at hotspots within these genes will be assessed via a SnapShot Cancer Mutation Panel. All patients originally diagnosed at Emory have this test performed as part of the routine neuropathologic assessment. We plan to use results from the original pathology report unless it was not performed; in which case, the original tumor tissue block will be obtained for this testing [Atif et al. 2015a; Atif et al. 2015b; Atif et al. 2019].
- **Genomic loss/gain particularly at the following loci (1p, 1q, 7p, 10q, 19q) –** Copy number variation of the entire genome will be assessed via the Oncoscan SNP Microarray Analysis. All patients originally diagnosed at Emory have this test performed as part of their routine neuropathologic

assessment. We will use results from the original pathology report unless it was not performed in which case the original tumor tissue block will be obtained for this testing.

Potential serum biomarkers (Research)

We propose to test a panel of circulating biomarkers to evaluate the effect of progesterone treatment on glioblastoma progression. The levels of these proposed biomarkers have been correlated with glioblastoma progression and survival in a number of clinical studies.

Serum will be obtained within 14 days prior to the start of treatment and at the 4 weeks blood draws after initiation of treatment. The initial and changes in levels of these biomarkers will be correlated with outcomes of patients on study to determine if there are detectable associations with response to progesterone. ELISA or Multiplexed fluorescent microsphere immunoassay will be performed to measure the levels of the following biomarkers:

- YKL-40 [Hormigo et al. 2006; Iwamoto et al. 2011]
- Matrix Meteloproteinase-9 (MMP-9) [Hormigo et al. 2006]
- Glial Fibrillary Acidic Protein (GFAP) [Jung et al. 2007]
- C-Reactive Protein (CRP) [Strojnik et al. 2014]
- Soluble CD14 [Zhou et al. 2010]
- Soluble CD23 [Zhou et al. 2010]

6. Data and Specimen Banking

Blood samples and GBM tumor specimen (paraffin block or unstained slides from previous surgery) will be obtained and used for medical research by the investigators of this study. *Data and specimens from this study may be useful for other research being done by investigators at Emory or elsewhere. To help further science, Investigators may provide de-identified data and/or specimens to other researchers. Any information that could identify participants will not be included. If data or specimens are labeled with study ID, we will not allow other investigators to link that ID to identifiable information.*

Samples and data collected under this protocol may be used to study **GBMs or other cancers**. Access to stored samples will be limited to IRB-approved investigators. Samples and data will be stored using codes assigned by the investigators or their designees. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.

All stored samples will be maintained in the laboratory to which it was sent initially for analysis and will be kept indefinitely unless destruction is requested by study participant or after conclusion of the study at such point where study investigators have deemed that there is no further use for the samples. Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking.

The results of some study tests and procedures will be used only for research purposes and will not be placed in subject's medical record. For this study, those items include: research blood assessment and research tumor specimen assessment.

7. Sharing of Results with Participants

In general, study staff will not provide any individual results to subjects (ex. outcome trial results or results from subject's samples studies). If something of urgent medical importance to the participating subjects will be found, the PI (or co-Is) will inform the subject, although we expect that this will be a very rare occurrence. Samples and data will only be used for research.

8. Study Timelines

The current plan is to complete enrollment to this study (up to 32 patients) over 2 years with up to 1 year additional followup time for a total of 3 years to enroll and follow patients per study specifications.

8.1 Duration of therapy

In the absence of treatment delays due to adverse event(s), patients will be treated up to 24 weeks until any one of the following:

- Tumor progression per protocol-specified criteria
- Death
- Unacceptable toxicity
- Symptomatic deterioration
- Investigator's decision to discontinue treatment
- Patient decision to discontinue treatment
- Patient withdraws consent
- Lost to follow up

In the event of a patient's withdrawal, the Investigator will make every effort to complete the End of Treatment procedures specified in the Schedule of Events.

Patients who are tolerating the drug with stable disease (SD) or better after 24 weeks of therapy may be considered for compassionate use continuation on a case-by-case basis after discussions between the patient, treating physician and the study supporter (IBSA Institut Biochimique SA, Lugano, Switzerland). It is at the discretion of the Investigator to continue treating patients in this circumstance as long as IBSA agrees to continue to provide drug until unacceptable toxicity, withdrawal by patient and/or treating physician or disease progression. Followup evaluations under these circumstances will be considered standard-of-care at the discretion of the patient's treating physician.

8.2 Duration of follow-up

Patients will be followed for approximately 4 weeks (to up to 6 weeks) after the last dose of study drug at which point they will have their end-of-study (EOS) visit. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

While patients will not undergo official visits for long-term follow-up after their EOS visit, further data for PFS and OS endpoints may be obtained based on chart review of standard-of-care visits with the subject's treating physician(s) unless the patient specifically request not to be followed in such fashion after coming off study.

Patient records may be reviewed until death to assess progression and survival. Survival information may be collected by clinic visit, email, or telephone after ending protocol treatment and until the study is terminated, the patient dies, or the patient is lost to follow-up.

A participant will be considered lost to follow-up if he fails to return for three scheduled visits and is unable to be contacted by the study site staff after three attempts at contact by phone.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.

Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

In case of a clinically significant AE, patient will be followed for safety until resolution or permanent sequelae of all toxicities attributable to study drug(s). If the patient discontinues study drug for a clinically significant AE, the patient will be followed until resolution of the AE or the event is considered to be stable and/or chronic.

9. Inclusion and Exclusion Criteria

Minorities and Women: Subjects will be approximately representative of the demographics of the patient population at Emory University. This study is designed to include women and minorities, but is not designed to measure specific sex differences of intervention effects. While males and females will be recruited with no preference to gender, and based on the results of previous studies, we expect 50% of our accrual to be female. No exclusion to this study will be based on race or sex. Minorities will actively be recruited to participate. However, based on previous enrollment, we expect about 35% of subjects to be minorities.

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	2	+	2	=	4
Not Hispanic or Latino	11	+	11	=	22
Ethnic Category: Total of all subjects	13	+	13	=	26
Racial Category					
American Indian or Alaskan Native	0	+	0	=	0
Asian	1	+	1	=	2
Black or African American	2	+	2	=	4
Native Hawaiian or other Pacific Islander	0	+	0	=	0
White	10	+	10	=	20
Racial Category: Total of all subjects	13	+	13	=	26

(A1 = A2) (B1 = B2) (C1 = C2)

Accrual Rate: 1-2 pts/month

Total Expected Accrual: 20 Min 26 Max

Projected Start Date of Study: April 1, 2021

Inclusion Criteria

- Patients must have pathologic confirmation of a glioblastoma or gliosarcoma diagnosis at initial surgery or second or later surgery.
- Patients may have had up to two previous salvage agents administered for treatment of recurrent GBM (may be at 1st, 2nd or 3rd recurrence).
- Patients must be ≥ 18 years of age.
- Patients must be able to have MRI scans for disease follow up.
- Recurrent GBM must consist of a minimum of 1 cm^3 of contrast enhancing disease on high resolution T1 post-contrast sequence as defined on pre-treatment MRI obtained within 14 days of initiating therapy. In the setting of recurrent GBM that was managed with surgery, there is no minimum disease required and the criteria for non-measurable/evaluable disease will be applied to determine imaging response (see Section 5.7).
- Patient must have the following lab values ≤ 14 days prior to registration:
    - WBC ≥ 3,000/µL
    - ANC ≥ 1,500/µL
    - platelet count of ≥ 75,000/µL (transfusion is not allowed within 1 week of a qualifying minimum platelet level to achieve eligibility)
    - hemoglobin ≥ 9.0 gm/dL (transfusion is allowed to reach minimum level)
    - AST/ALT ≤ 2.0x UNL
    - bilirubin ≤ 2 x UNL
    - creatinine ≤ 1.5 mg/dL
- Patients must have a life expectancy of ≥ 12 weeks.
- Patients must have a Karnofsky Performance Status (KPS) ≥ 60.
- Patients who are women of childbearing potential must have a negative pregnancy test documented ≤ 14 days prior to registration and agree to use adequate barrier contraceptive methods or abstinence for duration of study.
- Patients who are men must agree to not father a child while on study and agree to use adequate barrier contraceptive methods or abstinence for duration of study.
- Patients must be able to understand and provide written informed consent.
- Both men and women, and members of all races and ethnic groups are eligible for this trial. Subjects will be approximately representative of the demographics of the referral base for the participating institutions.
- Patient must not have a known allergy to progesterone.
- In females, no active vaginal bleeding.
- Patients may not be enrolled on any other therapeutic trial for which they are receiving an anti-tumor therapy.

Exclusion Criteria

- Patients with pacemakers, aneurysm clips, neurostimulators, cochlear implants, metal in ocular structures, history of being a steel worker, or other incompatible implants which makes MRI safety an issue are excluded.

- Patients that have any significant medical illnesses that in the investigator's opinion cannot be adequately controlled with appropriate therapy or would compromise the patient's ability to tolerate this therapy are excluded.
- Patients with uncontrolled hypertension
- Patients with a history of severe hepatic dysfunction of disease, liver tumors or any active liver disease are excluded.
- Patients with a history of idiopathic jaundice, severe pruritis and pemphigoid gestastationis during pregnancy are excluded.
- Patients with a history of breast or genital tract cancer are excluded.
- Patients with a history of any other invasive cancer (except non-melanoma skin cancer and excluding carcinoma in-situ), unless in complete remission and off all therapy for that disease for ≥ 3 years, are ineligible.
- Patients with an active infection or serious intercurrent medical illness are ineligible.
- Patients who have received any radiation therapy within 4 weeks (for recurrent GBM) or 90 days (for initial diagnosis of GBM) of the start of progesterone therapy are ineligible.
- Patients who received any other in anti-tumor agents (including investigational anti tumor agents, but excluding avastin) must be off therapy for 4 weeks prior to initiating progesterone on study. Patients on avastin at enrollment will be allowed to be maintained on their current dose of avastin when they begin progesterone. Patients receiving anti-coagulation therapy are excluded.
- Patients that underwent resection for their recurrent GBM need to wait at least 4 weeks before they can initiate progesterone treatment.
- Patients with active or recent (within 6 months) thromboembolic disease are excluded.
- Patients with current ongoing therapy with estrogen/progesterone (including hormonal contraceptives) are excluded. Would need to stop this form of birth control at least 7 days prior to initiation of therapy to be eligible.

10.Local Number of Participants

We will be recruiting all participants (up to 32 patients) at the Winship Cancer Institute of Emory University. Patients will be registered after signing of the informed consent document and meeting all entry requirements.

11.Recruitment Methods

Subjects will be recruited from recurrent GBM patients referred by neurosurgery, neuro-oncology or radiation oncology. Initial screening will be conducted/reviewed by clinical investigators and/or their trained designee (e.g. research nurse, research coordinator, etc.). Cases will be identified from the neurosurgery/neuro-oncology/radiation oncology outpatient clinics or neurosurgery/oncology inpatient services. After potential subjects have been identified, their clinical care team at Winship will inform potential subjects about the known benefits and potential risks of a clinical trial as well as other available treatment options.

Some of the subjects recruited for this protocol will be patients being treated at Emory and under the care of one or more of the study investigators. Some potential subjects will be identified by their treating physician and referred to Emory for possible participation in the protocol.

No incentives are provided to patients for trial participation.

Study personnel will notify Winship Central Subject Registration (WCSR) by email at winshipcsr@emory.edu, once subject has been consented for a trial.

Email notification must be done within 24 hours after consent has been obtained and it will include scanned copies of:

- Signed patient consent form (which includes a HIPAA authorization component)
- Emory Research Management System (ERMS; *https://erms.emory.edu*) Enrollment Fax Cover

The WCSR will enter the subject into the OnCore Research Management System, which is the system of record for Winship Cancer Institute Clinical Trials.

Enrolling a subject requires careful screening and determination of eligibility.

Eligible patients will be enrolled on study centrally at Winship Cancer Institute by the Study Coordinator.

When all required test results are available, complete the eligibility checklist and provide the checklist and the supporting documentation to the IRB-approved investigator for review and sign-off. This eligibility checklist is to be verified by 2 people (the investigator and CRN/CRC). Once the investigator (sub-investigator, Co-Investigator) has signed the eligibility checklist, enrollment may proceed. OnCore and ERMS must be updated to reflect eligibility and on treatment status.

Following enrollment, patients should begin protocol treatment within 5 business days. Issues that would cause treatment delays should be discussed with the Principal Investigator.

12.Withdrawal of Participants

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Any specific contraindication for use of progesterone (e.g. thromboembolic event)
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- If the treating physician feels that doing so would be in the best interest of the patient
- Participant unable to receive progesterone for > 14 days

The reason for participant discontinuation or withdrawal from the study will be recorded on the study Case Report Form (CRF). Subjects who sign the informed consent form but do not receive the study intervention may be replaced. Subjects who sign the informed consent form and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will be replaced only if they receive less than 28 days of progesterone.

13.Risks to Participants

Risks associated with additional blood draws. There are some additional blood draw for research purposes (e.g. PK evaluations, when required, and serum biomarkers) that may be required. The physical risk of drawing blood is local pain and bruising at the site of venipuncture. Qualified phlebotomists or designee will draw blood samples. Care will be taken to obtain these specimens in a safe and hygienic manner. A small number of people experience lightheadedness or fainting. There is a slight risk of infection. To minimize these risks, attempts will be made to draw study blood samples at the same time as blood draws needed for routine clinical care are obtained. Repeated blood drawing may be associated with iron deficiency anemia.

Data security- Subjects will be asked to provide personal health information (PHI). All attempts will be made to keep this PHI confidential within the limits of the law. However, there is a chance that unauthorized persons will see the subjects' PHI. All records will be kept in a locked file cabinet or maintained in a locked room at the participating sites. Electronic files will be password protected behind an academic institutional firewall. Only people who are involved in the conduct, oversight, monitoring, or auditing of this study will be allowed access to the PHI that is collected. Any publications from this study will not use information that will identify subjects. Organizations that may inspect and/or copy research records maintained at the participating sites for quality assurance and data analysis include groups such as the National Cancer Institute (NCI) and Food and Drug Administration (FDA).

Risks associated with daily subcutaneous drug injections. There are potential risks from the daily injection of drug including injection site reactions (irritation, pain, pruritis, and swelling). Infection can also potentially develop. Potential effects of the drug is documented below.

Risks associated with administration of natural progesterone. Potential effects of the drug are documented below. The list shows what has been previously established for subcutaneous progesterone; which is an aqueous formulation currently available in Europe.

As per the manufacturer of subcutaneous progesterone (IBSA Institut Biochimique SA), repeated doses of progesterone may have the following side effects:

Undesirable effects: The most frequently reported adverse drug reactions during treatment with subcutaneous progesterone during clinical trial are administration site reactions, breast and vulvo-vaginal disorders. The table below displays the main adverse drug reactions in women treated with subcutaneous progesterone in the pivotal clinical trial. Data are expressed by system organ class (SOC) and frequency.

Overdose: High doses of progesterone may cause drowsiness. Treatment of overdose consists of discontinuation of subcutaneous progesterone together with initiation of appropriate symptomatic and supportive care.

System Organ Class (SOC)	Very common (≥ 1/10)	Common (≥ 1/100 to< 1/10)	Uncommon (≥ 1/1000 to< 1/100)
Psychiatric disorders			Mood altered
Nervous system disorders		Headache	Dizziness Somnolence

Gastrointestinal disorders		Abdominal distension Abdominal pain Nausea Vomiting Constipation	Gastrointestinal disturbances
Skin and subcutaneous tissue disorders			Pruritus Rash
Reproductive system and breast disorders	Uterine spasm Vaginal haemorrhage	Breast tenderness Breast pain Vaginal discharge Vulvo-vaginal pruritus Vulvo-vaginal discomfort Vulvo-vaginal infl OHSS	Breast disorders
General disorders and administration site conditions	Administration site reactions*	Injection site haematoma Injection site induration Fatigue	Feeling hot Malaise Pain

*Administration site reactions, such as irritation, pain, pruritus and swelling.

(Reference: https://www.assistingnature.gr/wp-content/uploads/2017/07/Prolutex.pdf)

14.Potential Benefits to Participants

While pre-clinical evidence suggests possible anti-GBM activity for progesterone and one of the primary objectives of this study is to measure objective response at the 8 week MRI, there is no guarantee of benefit to subjects who enroll in this protocol.

15.Data Management and Confidentiality

15.1 Statistical consideration section: Biostatistician

This is a single arm, Phase 1 study, designed to evaluate the pharmacokinetics, safety/tolerability and efficacy of subcutaneously administer natural progesterone in subjects with recurrent glioblastoma (GBM). The study consists of two parts: Part 1) Dose finding phase; Part 2) Dose expansion phase.

Statistical design and sample size:

Dose finding phase (Part 1):

The dose finding phase will proceed using a standard 3+3 approach in order to identify the maximum tolerated dose (MTD). The study will start at Dose Level 0 with dose moving according to protocol criteria

(**Section 5.2**). For the 3+3 dose finding phase, a dose limiting toxicity (DLT) will be defined as a grade 3 or

greater toxicity that is not clearly due to the underlying disease or extraneous causes that develops in the first 28 days of starting progesterone (exceptions as noted in **Section 5.3**). Dose levels are shown on the following table:

Dose Level	Daily subcutaneous dose (mg)
-1	25
0	50
1	75

After treatment initiation of up to 6 patients at a dose level and continuation for a minimum of 4 weeks with AE assessment, enrollment to the next (higher or lower) dose level as determined by the rules will only start after data is presented to the Winship Data Safety Monitoring Committee (DSMC) and final approval is obtained for starting the next dose level. The sample size in the dose finding phase will range from 6-12.

Dose expansion phase (Part 2):

A total of 20 patients will be enrolled at the MTD (including those in the Dose finding phase at this dose level) in the dose expansion phase unless futility criteria for the expansion cohort is met. The MTD from the dose finding phase (25 mg, 50 mg, or 75 mg) administered subcutaneously 1x/day will be given in this expansion cohort until 20 patients have initiated the dose determined from the dose finding phase. The objective of the dose expansion phase is to provide a preliminary efficacy assessment, and thus no further justification for this sample size is required.

Futility analysis - As mentioned above, there will be one interim analysis for futility. It is known that random ineffective therapies for recurrent GBM may still produce a response rate of 10%. Therefore, the overall response rate (ORR) for first 10 patients (1/2 of planned expansion cohort size) that undergo treatment with the subcutaneous progesterone at the final dose from the dose finding phase of the study will be determined. If the ORR at the 8 week assessment time point is 20% (2 of 10) or greater, then the study will be declared potentially non-futile and enrollment of the full expansion cohort (N=20) will proceed. If the ORR at this time point is 10% (1 of 10) or less, then the study will be declared futile and further enrollment will be aborted. If the study is declared futile at this interim analysis, new enrollment will be discontinued but any patients that is still on therapy at that time will be allowed to continue therapy as long as they meet criteria to continue therapy as defined in Section 8.1 (e.g. continue to not have protocol-specified progressive disease).

Analysis populations:

Safety population: All subjects enrolled in the study who received the study drug.
Efficacy population: Subjects enrolled in the study who received the study drug at the expansion dose from both the dose finding and expansion phases of study.

Data analysis plan for each objective is listed below:

Primary Objectives

Dose finding phase (Part 1):

- *To determine the safety of administering daily subcutaneous natural progesterone for the treatment of patients with recurrent GBMs.* The safety of this approach will be confirmed by assessing toxicity potentially attributable to the daily progesterone treatment. Toxicity will be determined by CTCAE v5.0 criteria. The MTD will be determined using the standard 3+3 approach. **Dose escalations will be reviewed by the Winship Data Safety Monitoring Committee (DSMC) (per Winship SOP 7.9 Dose Escalation Determinations for Sponsor-Investigator or Investigator Initiated Studies). The PI or designee will provide an update on all relevant safety data of patients entered to a dose level to the DSMC when dose escalation is planned. Upon obtaining approval from the DSMC, dose escalation can proceed.**

- *To determine the pharmacokinetics of natural progesterone given to recurrent GBM patients by subcutaneous injection.* This analysis will be performed to determine what plasma drug levels can be achieved in recurrent GBM patients with subcutaneous administration of natural progesterone and whether this is in line with what was previously determined in healthy subjects.

Dose expansion phase (Part 2):

- *To determine the overall response rate (ORR) of eligible patients with recurrent GBM treated with daily subcutaneous natural progesterone*. This primary analysis will be performed on all patients treated at the expansion dose (from either the dose finding or expansion phases). In particular, we will be looking for the fraction of patients that are able to maintain at least stable disease (SD), given our expectation that, for patients showing a contrast enhancing recurrence, all will continue to progress unless they are receiving an effective therapy. ORR will be reported, and an exact 95% confidence interval will be reported using the Clopper-Pearson method. There will be one interim analysis for futility that is described above that may halt enrollment before full accrual of the expansion cohort.

Secondary Objectives

Dose expansion phase (Part 2):

- *To determine and compare the progression free survival of eligible patients with recurrent GBM*. Patients on this study will be followed for progression free survival (PFS), which is defined from the time of pre-treatment MRI to the time of either radiographic progression or death, whichever occurs first. Both actuarial PFS curves and 24-week PFS (for expansion dose patients and all patients as separate analyses) will be estimated using the Kaplan-Meier method, and compared to matched historical controls using log-rank tests and univariate Cox proportional hazards models. The matched effects will be estimated by a Cox model with a robust variance estimator. A 95% confidence interval will be provided for 24-week PFS using the Greenwood formula to estimate the standard error.

- *To determine and compare the overall survival of eligible patients with recurrent GBM*. Patients on this study will be followed for overall survival (OS) which is defined from the time of pre-treatment MRI to the time of death. Both actuarial OS curves and 24-week OS (for expansion dose patients and all patients as separate analyses) will be estimated using the Kaplan-Meier method, and compared to matched historical controls using log-rank tests and univariate Cox proportional hazards models. The matched effects will be estimated by a Cox model with a robust variance estimator. A 95% confidence interval will be provided for 24-week OS using the Greenwood formula to estimate the standard error.

Exploratory Objectives:

Dose expansion phase (Part 2):

- *To determine whether progesterone receptor levels within the tumor correlates with response to daily subcutaneous natural progesterone.* This will be examined for both expansion dose patient and all patients as separate analyses. Original tumor and any recurrent tumor samples will be assessed for progesterone receptor expression levels by immunohistochemistry and these results will be correlated with response assessment to determine whether there is any correlation. Progesterone receptor staining by IHC will be scored on a scale of 0-4 by standard criteria and then compared with response assessment using standard statistical tests such as two sample t-tests or Mann-Whitney U tests, where appropriate, to determine whether there is any correlation between expression level and response.
- *To determine if other intrinsic tumor factors (mutations and genomic loss/gains, see **Section 5.7** for specific details) correlates with response to daily subcutaneous natural progesterone.* This will be examined for both expansion dose patient and all patients as separate analyses. Each of the tumor mutational and genomic loss/gain factors will be scored and these results will be correlated with response assessment using chi-square tests or Fisher's exact tests, where appropriate.
- *To determine if the absolute values or changes in the level of serum biomarkers (see **Section 5.7** for specific biomarkers) correlates with response to daily subcutaneous natural progesterone.* This will be examined for both expansion dose patient and all patients as separate analyses. Each of these serum biomarkers will be quantitated at the specific time points (pre-treatment and 4 weeks) with specific levels and changes in levels recorded. These results will be correlated with response assessment using two sample t-tests or Mann-Whitney U tests, where appropriate.
- *To determine the quality-of-life (QOL) by validated instruments of eligible patients with recurrent GBM.* This will be examined for both expansion dose patient and all patients as separate analyses. Serial QOL assessments will be determined in patients and compared with historical cohorts to determine whether there is any difference in patients treated with subcutaneous progesterone for recurrent GBM. Linear mixed effects models will be applied to model the repeatedly measured score from each assessment and/or test over time. We hypothesize that response to progesterone will correlate with positive effects on the temporal changing patterns in the scores on the QOL assessments. We will follow the recent guidelines of the American Statistical Association on reporting p-values and their meaning [Wasserstein and Lazar 2016; Wasserstein et al. 2019]

Safety assessment:

Adverse event stopping rule including interim analysis: Safety assessments will be performed throughout treatment, at weekly intervals during the 1st 4 weeks and at the beginning of every 4 weeks interval thereafter until patient comes off study. In the dose finding phase, stopping rules are described above. Besides the toxicity assessment of 3-6 patients at a dose level in the dose finding phase, toxicity will be assessed during the dose expansion phase on an ongoing basis. If, at any time, the aggregate rate of treatment-related toxicities meeting DLT criteria exceeds 33% across all subjects treated in the expansion cohort, the findings will be discussed and further enrollment may be interrupted. Depending on the nature and grade of the toxicity and after assessing the risk:benefit ratio, a new dose(s) for all cohorts may be initiated at a previously tested lower dose level, or at a dose level intermediate to previously tested lower dose levels.

15.2 Data/specimens:

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Principal Investigator. The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Data and/or data forms will be submitted in the clinical management system - Online Collaborative Research Environment (ONCORE)- per Winship SOP 4.2 Data Completion Metrics.

All information in original records and certified copies of original records or clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the trial is considered source data. Source data are contained in source documents, which can be original records or certified copies of hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries of evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. Case Report Forms (CRFs) - Source data may be collected in the source documents or entered directly onto the case report forms.

All documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence will be maintained for at least 2 years after the investigation is completed.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

Samples and data collected under this protocol may be used to study GBMs and other cancers. Access to stored samples will be limited to IRB-approved investigators. Samples and data will be stored using codes assigned by the investigators or their designees. Data will be kept in password-protected computers. Only investigators will have access to the samples and data. All stored samples will be maintained in the laboratory to which it was sent initially for analysis. Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking.

16.Provisions to Monitor the Data to Ensure the Safety of Participants

Definition of Adverse Events (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)). An adverse event can be any unfavorable and unintended sign (e.g., including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the drug, whether or not it is considered to be drug related. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of drug.

Definition of Serious Adverse Events (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- **Death**
- **Life-threatening adverse event** - Life-threatening means that the patient was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- **Inpatient hospitalization or prolongation of existing hospitalization** - Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered AEs if the illness or disease existed before the patient was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (eg, surgery performed earlier than planned).
- A **persistent or significant disability/incapacity** or substantial disruption of the ability to conduct normal life functions, or 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 participant 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).

Classification of an Adverse Event

<u>Severity of Event</u>

Most adverse events (AEs) will be graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (grade 1-5). For AEs not included in CTCAE, the following guidelines will be used to describe severity to match the CTCAE grading scale.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".
- **Life-threatening –** Events result in the patient being at immediate risk of death from the reaction as it occurred.
- **Death**

<u>Relationship to Study Intervention</u>

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The

degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely Related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

Adverse Event and Serious Adverse Event Reporting

Expectedness

Principal Investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

Adverse Event Reporting

From the time of treatment allocation/randomization through **28** days following cessation of treatment, all adverse events, that begin or worsen after informed consent, **must be recorded** by the investigator or designee at each examination on the Adverse Event case report forms/worksheets.

The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF/worksheet.

Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Grade 1 to 5 will be used to characterize the severity of the Adverse Event.

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, life-threatening, and death related to the AE corresponding respectively to Grades 1 - 5, will be used. Information about any deaths (related to an Adverse Event or not) will also be collected through a Death form (or EOT/SEC/Survival Information in NOVDD). The occurrence of adverse events should be sought by non-directive questioning of the patient (patient) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (patient) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-5)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes) or Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes, investigational treatment, Yes, the study treatment (non-investigational), Yes, both and/or indistinguishable)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Whether it is serious, where a serious adverse event (SAE) is defined above (**Section 16**) and which seriousness criteria have been met (include for NCDS trials).
7. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)

If the event worsens the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4. For phase I studies any AE that constitutes a DLT should be reported like a grade 3 and 4 adverse event. All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome. Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per protocol-specified criteria for GBMs), should not be reported as a serious adverse event.

Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

Serious Adverse Event Reporting

For the time period beginning at treatment allocation/randomization through **28** days following cessation of treatment, or **28** days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause whether or not related to the study drug, must be **submitted on an SAE form** and assessed by PI in order to determine reporting criteria to IRB, DSMC, FDA, supporter or IND Sponsor.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the IND sponsor and should be provided as soon as possible. The IND sponsor-investigator (Hui-Kuo G. Shu) will be responsible for notifying FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

All Serious Adverse Events which occur during all periods of a clinical trial, independently of causal relationship, **must be reported immediately (i.e. within 24 hours after first knowledge)** by fax or email to:

IBSA – Drug Safety Unit
Tel +41 58 360 1669
Fax +41 58 360 1695
Email: farmacovigilanza@ibsa.ch

Actions in case of SAE/SAR:

When the Investigator receives knowledge of an SAE he/she is expected to proceed as follows:

1. Take the appropriate diagnostic and therapeutic measures to minimize the risk for the subject
2. Collect evidence for the elucidation of the relationship between SAE and the IMP
3. Fill in, in a clear and legible way, the SAE form (Type of report: initial) with all the information requested and fax or email it to IBSA - Drug Safety Unit within 24 hours after first knowledge,
4. Contribute to clarification of the cause(s) of the SAE and to the assessment of potential risk by providing any relevant information obtained or requested with respect to the case.

The preliminary notification should include, at least this information:

1. Protocol number and EUDRACT number (if applicable);
2. Subject's identification (screening/randomization number, age if applicable by the law-, gender), relevant medical history and any concomitant medications taken during the study,
3. SAE/event description and its onset;
4. Investigator's causality assessment on the event relationship with the study medication;
5. IMP name and batch N°, date of first and last dosing before SAE, if code was broken – when applicable;
6. Detail at best the circumstances leading to SAE occurrence and, in case of unblinding, detail the reason for the code to be broken;

7. Specific treatment of the SAE;
8. Investigator: name, address, phone number.

All subjects with serious adverse events must be followed up for outcome.

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported to **IBSA-DSU** by e-mail as follow-up to the original episode **within 48 hours** of the investigator receiving the follow-up information. A new SAE form will be completed for this and the "Follow-up" box (second page) ticked.

An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Any SAEs experienced after the reporting period described above should only be reported to FDA (per IND Sponsor-Investigator requirements)/IRB (IRB reporting requirements) if the investigator suspects a causal relationship to the study treatment.

Information about all SAEs is collected and recorded on the **Serious Adverse Event Report Form**; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form, and submit the completed form.

Each reoccurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or withdrew from study participation.

The Emory IRB, will be notified of adverse events per their reporting requirements. Written IND safety reports will be submitted to the FDA by the IND sponsor-investigator, for serious, unexpected suspected adverse reactions within 15 calendar days of learning of its occurrence. If the event is fatal or is deemed to be life threatening, the report will be made within 7 calendar days. The IND sponsor-investigator will also make an assessment of whether the event constitutes an unanticipated problem posing risks to subjects or others (UP). This assessment will be provided to the Emory University IRB, which, in turn will make a final determination. If the Emory IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

All SAEs for drug studies must be recorded on a MedWatch 3500 Form. SAE reports and any other relevant safety information are to be forwarded to the following:

MedWatch 3500 Reporting Guidelines:

Note: MedWatch 3500 forms and other information related to MedWatch reporting are available at http://www.fda.gov/medwatch/index.html.

A copy of all 15 Day Reports and Annual Progress Reports is submitted to **the FDA** as required by FDA as well as to the study-supporter, IBSA. Investigators will cross reference this submission according to local regulations to the Investigational Compound Number (IND, CSA, etc.) at the time of submission.

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 5.0. Any adverse event which changes CTCAE grade over

the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets. All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

Reporting Requirements for IND holder

For Investigator-sponsored IND studies, reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR, Part 312.32. Events meeting the following criteria need to be submitted to the FDA as Expedited IND Safety Reports.

7 Calendar-Day Telephone or Fax Report

The Sponsor-Investigator is required to notify the FDA of a fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the use of *investigational agents*. An unexpected adverse event is one that is not already described in the most recent Guidance for Investigator section of the Investigator's Brochure. Such reports are to be telephoned or faxed to the FDA, within 7 calendar days of the first learning of the event.

15 Calendar-Day Written Report

The Sponsor-Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious unexpected adverse event that is considered reasonably or possibly related to the use of investigational agent.

Written IND Safety Reports with analysis of similar events are to be submitted to the FDA, within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500 Form but alternative formats (e.g., summary letter) are acceptable.

FDA Fax number of IND Safety Reports: 1-(800)-FDA-1078.

The IND sponsor-investigator will also make an assessment of whether the event constitutes an unanticipated problem posing risks to subjects or others (UP). This assessment will be provided to the Emory University IRB, which, in turn will make a final determination. If the Emory IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

All Adverse Events will be reported to regulatory authorities, IRBs and investigators in accordance with all applicable global laws and regulations.

Coordinating center reporting to the Food and drug administration (FDA)

The Sponsor Investigator, as holder of the IND (as applicable), will be responsible for all communication with the FDA. The Sponsor Investigator [or designee] will report to the FDA, regardless of the site of occurrence, any adverse event that is serious, unexpected and reasonably related (i.e., possible, probable, definite) to the study treatment.

Unexpected fatal or life-threatening experiences associated with the use of the study treatment will be reported to FDA as soon as possible but no later than 7 calendar days after initial receipt of the information.

All other serious unexpected experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 15 calendar days after initial receipt of the information. Events will be reported to the FDA by telephone (1-800-FDA-1088) or by fax (1-800- FDA-0178) using

MEDWATCH Form FDA 3500A (Mandatory Reporting Form for investigational agents). Forms are available at http://www.fda.gov/medwatch/getforms.htm.

An annual safety report containing all SAEs, expected and unexpected, will be sent to the FDA and other applicable regulatory authorities.

Second and secondary malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

All secondary malignancies that occur following treatment with an agent under an IND/IDE must be reported through **ONCORE.**

Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy).

Definition of unanticipated problems (UP) and reporting requirements

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or an outcome that meets **all** the following criteria: Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied; Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. This study will use the OHRP definition of unanticipated problems. Incidents or events that meet the OHRP criteria for UPs require the creation and completion of a UP report form. It is the site investigator's responsibility to report UPs to their IRB and to the DCC/study sponsor. The UP report will include the following information: Protocol identifying information: protocol title and number, PI's name, and the IRB project number; A detailed description of the event, incident, experience, or outcome; An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP; A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP. The IND sponsor-investigator will make an assessment of whether the event constitutes an unanticipated problem posing risks to subjects or others (UP). This assessment will be provided to the Emory University IRB. If the Emory IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

The Data and Safety Monitoring Committee (DSMC)

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will provide oversight for the conduct of this study. The DSMC functions independently within Winship Cancer Institute to conduct internal monitoring functions to ensure that research being conducted by Winship Cancer Institute Investigators produces high-quality scientific data in a manner consistent with good clinical practice (GCP) and appropriate regulations that govern clinical research. Depending on the risk level of the protocol, the DSMC review may occur every 6 months or annually. For studies deemed High Risk, initial study monitoring will occur within 6 months from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. For studies deemed Moderate Risk, initial study monitoring will occur within 1 year from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. Subsequent monitoring will occur in routine intervals per the Winship Data and Safety Monitoring Plan (DSMP).

The DSMC will review pertinent aspects of the study to assess subject safety, compliance with the protocol, data collection, and risk-benefit ratio. Specifically, the Winship Cancer Institute Internal Monitors assigned to the DSMC may verify informed consent, eligibility, data entry, accuracy and availability of source documents, AEs/SAEs, and essential regulatory documents. Following the monitoring review, monitors will provide a preliminary report of monitoring findings to the PI and other pertinent individuals involved in the conduct of the study. The PI is required to address and respond to all the deficiencies noted in the preliminary report. Prior to the completion of the final summary report, monitors will discuss the preliminary report responses with the PI and other team members (when appropriate). A final monitoring summary report will then be prepared by the monitor. Final DSMC review will include the final monitoring summary report with corresponding PI response, submitted CAPA (when applicable), PI Summary statement, and available aggregate toxicity and safety data.

The DSMC will render a recommendation and rating based on the overall trial conduct. The PI is responsible for ensuring that instances of egregious data insufficiencies are reported to the IRB. Continuing Review submissions will include the DSMC recommendation letter. Should any revisions be made to the protocol-specific monitoring plan after initial DSMC approval, the PI will be responsible for notifying the DSMC of such changes. The Committee reserves the right to conduct additional audits if necessary.

The PI or designee must provide the DSMC a report outlining the overall enrollment and path to decision for the escalation dose(s) selected.

Additional points in regards to the DSMP specifically for this study:

- After the first subject has enrolled, monthly research meeting will be held by the PI along with selected members of the study team to review toxicity and efficacy data as they are acquired.
- AEs (including SAEs) will be recorded based on planned assessment time points by the CRC and assessed by the PI/sub-investigators according to SOP. These will then be reviewed on an ongoing basis at the monthly research meeting with reports to the DSMC at appropriate times (e.g. to initiate next dose level).
- Oversight of the study team will be carried out at neuro-oncology working group meeting and will include random checks of CRFs/charts.
- Study team will be trained on study procedures at a study initiation meeting prior to study opening. Changes to the study (e.g. Study Amendments) will be communicated to the entire study team by e-mail with documentation that team members acknowledgement their understanding of the changes.

17. Provisions to Protect the Privacy Interests of Participants

Participants will be assured of their voluntary participation in the study, their choice to answer or not answer any question, and the protocol for maintaining confidentiality.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

18. Economic Burden to Participants

The study supporter (IBSA) will be providing the study drug for no charge on this study but will not pay for other items and services the subject may receive in this study. Funds associated with this study will be available to cover the cost of research only studies (e.g. the PK and serum biomarker assessments). Subjects will have to pay for the items or services for which the study supporter or the study itself does not pay. The study supporter and the study itself will not pay for regular medical care. If subjects have insurance, Emory will submit claims to the insurance for items and services that the are not covered by the study supporter or the study itself. Emory will send in only those claims for items and services that it reasonably believes the insurance will pay and that will not be paid by the study supporter or the study itself. The actual amount that participants have to pay depends on whether or not they have health insurance and whether or not that insurance will pay for any research study costs. Generally, insurance companies will not pay for items and services that are required just for a research study. Some insurance companies will not pay for regular medical treatment or treatment for complications if in a study. If subject do not have insurance, Emory will review that particular case as part of its program for low-income patient care. The standard policies of that program will apply. The program will figure out if subjects have to pay any costs for taking part in the study and what those costs will be.

19. Consent Process

The initial informed consent discussion will occur in Winship Cancer Institute or the Emory Clinic.

At Winship Cancer Institute, the informed consent is an ongoing, interactive process rather than a one-time information session. The consent form document is designed to begin the informed consent process, which provides the patient with ongoing explanations that will help them make educational decisions about whether to begin or continue participating in the trial. The research team knows that a written document alone may not ensure that the patient fully understands what participation means. Therefore, the research team will discuss with the patient the trial's purpose, procedures, risks and potential benefits, and their rights as a participant. The team will continue to update the patient on any new information that may affect their situation.

Consent will be obtained prior to any research-driven procedures. The investigator will assess the patient's capacity during his/her encounters with him or her. The investigator will give the person providing consent adequate opportunity to read the consent document before it is signed and dated.

It will be explained to prospective participants that the study involves research, the purpose of the research, the expected duration of participation, as well as the approximate number of participants to be enrolled. The study procedures, and identification of research procedures v. non-research will also be thoroughly discussed. It will be explained to participants that participation is voluntary and that the subject may discontinue at any time.

Refusal to participate or withdraw will not involve a penalty or loss of benefits to which the participant is otherwise entitled. Refusal will in no way affect the participant's future are. The participant will also be told of the possible consequences of the decision to withdraw from the research, and procedures for orderly termination of participation.

Any significant new findings developed during the course of the research that may affect the participant's willingness to continue to participate will be provided. Also explained will be anticipated circumstances under which the subject's participation may be terminated by the investigator without the participant's consent.

Prospective participants will be provided with a description of any reasonably forseeable risks or discomforts as well as a description of any benefits to the participant or to others that might be reasons expected from the research. Alternative procedures or courses of treatment will also be thoroughly discussed.

Prospective participants will also be given detailed information describing the extent to which confidentiality of records identifying the participant will be maintained and what records may be examined by the research staff, IRBs, sponsor, their representatives, and possibly the FDA or OHRP.

Also communicated to the participant will be an explanation that emergency medical care will be arranged for a study-related illness or injury, and an explanation of whether funds are set aside to pay for this care and/or compensation, and if so by whom (e.g., sponsor, subject, insurer). The participant is told the source of the study's funding.

All participants will be told of any additional costs that may result from participation in the research.

Consent will be done in person or remotely through secured email, phone or by electronic consenting using one of the methods that is Emory LITS approved (e.g. DocuSign). We will follow Emory's guidance on use of electronic informed consent.

Non-English-Speaking Participants

A certified translator/interpreter will be present during the consenting process and all questions and concerns will be answered by the treating physician.

A Short Form in that specific language will be used. A certified translator/interpreter will be present during the consenting process and this will be documented. We will use what's available on Emory IRB website. For

the languages that are not available, we will have the short form translated to that language and submit the IRB for review and approval prior to use. Process to Document Consent in Writing: Winship SOP 2.1: ”Obtaining Informed consent for Interventional clinical trial” will be followed.

Participants who are not yet adults (infants, children, teenagers)

N/A

Cognitively Impaired Adults

N/A

Adults Unable to Consent

A legally authorized representative may take part in the informed consent discussion sign the consent form on behalf of the patient. We will follow Emory IRB P&P in regards to use of LAR.

Waiver or Alteration of Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception)

N/A

20. Setting

The research will be conducted at the Winship Cancer Institute of Emory University.

Potential participants will be identified in the clinics for neuro-oncology, neurosurgery, radiation oncology or multidisciplinary brain tumor care as well as at the weekly Adult Brain Tumor Conference at Emory University.

21. Resources Available

Emory University was founded in 1836 and is a national center for teaching, research, and service. Emory University has been named as one of the nation’s top 25 universities for more than a decade by the U.S. News and World Report. Emory University research partners include the Georgia Institute of Technology, the University of Georgia, Morehouse School of Medicine, the US Centers for Disease Control and Prevention, Children's Healthcare of Atlanta, and the Georgia Clinical and Translational Science Alliance (GACTSA). Emory University researchers received $734 million from external funding agencies in fiscal year 2018, including approximately $441 million in funding from federal agencies, $359 million of this from the National Institutes of Health (NIH).

Winship Cancer Institute (Winship) is Georgia's first and only National Cancer Institute (NCI)-designated Comprehensive Cancer Center (P30CA138292) and is dedicated to the integration of innovative clinical and basic science research with outstanding patient care for the prevention, treatment and control of cancer. First designated in 2009, Winship’s NCI designation was renewed in 2012 and 2016, achieving an “outstanding” rating. Winship earned the prestigious Comprehensive Cancer Center designation from the

NCI in 2016, after demonstrating that its outstanding programs are reducing the cancer burden on the state of Georgia through research conducted in its laboratories, its clinical trial program, and its population-based science. The institutional support for Winship was rated as 'exceptional' by the review panel.

The **Winship Clinic Building C** houses the primary offices and clinical space for cancer services including the medical oncology, hematology, and surgical oncology clinics, the radiation oncology program, and the Winship Ambulatory Infusion Center. In summer 2017, Emory Healthcare completed the expansion of **Emory University Hospital Tower** on Clifton Road. This nine-floor facility adds 144 inpatient beds to the hospital, of which more than 80% are dedicated to cancer care. The hospital expansion also accommodates cancer patient-specific intensive care units, an expanded BMT Unit with peri-transplant clinics to facilitate continuity of care, and a 24-hour cancer urgent care center, which serves as both a triage facility and short stay treatment center for patients with cancer-related medical concerns.

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APPENDIX 1 PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

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APPENDIX 2 QOL Questionnaires

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Your birthdate (Day, Month, Year): ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Today's date (Day, Month, Year): 31 ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

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ENGLISH

EORTC QLQ - BN20

Patients sometimes report that they have the following symptoms. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
31.	Did you feel uncertain about the future?	1	2	3	4
32.	Did you feel you had setbacks in your condition?	1	2	3	4
33.	Were you concerned about disruption of family life?	1	2	3	4
34.	Did you have headaches?	1	2	3	4
35.	Did your outlook on the future worsen?	1	2	3	4
36.	Did you have double vision?	1	2	3	4
37.	Was your vision blurred?	1	2	3	4
38.	Did you have difficulty reading because of your vision?	1	2	3	4
39.	Did you have seizures?	1	2	3	4
40.	Did you have weakness on one side of your body?	1	2	3	4
41.	Did you have trouble finding the right words to express yourself?	1	2	3	4
42.	Did you have difficulty speaking?	1	2	3	4
43.	Did you have trouble communicating your thoughts?	1	2	3	4
44.	Did you feel drowsy during the daytime?	1	2	3	4
45.	Did you have trouble with your coordination?	1	2	3	4
46.	Did hair loss bother you?	1	2	3	4
47.	Did itching of your skin bother you?	1	2	3	4
48.	Did you have weakness of both legs?	1	2	3	4
49.	Did you feel unsteady on your feet?	1	2	3	4
50.	Did you have trouble controlling your bladder?	1	2	3	4

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Date: ☐☐ / ☐☐ / ☐☐
(month) (day) (year)

Subject Initials: ☐☐☐

Study Name: _____
Protocol #: _____
PI: _____

MD Anderson # : ☐☐☐☐☐☐

PDMS # : ☐☐☐☐

M. D. Anderson Symptom Inventory - Brain Tumor (MDASI - BT)

Part I. How severe are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been in the last 24 hours. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
1. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
2. Your **fatigue (tiredness)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
3. Your **nausea** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
4. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
5. Your feeling of being **distressed (upset)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
6. Your **shortness of breath** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
7. Your problem with **remembering things** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
8. Your problem with **lack of appetite** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
9. Your feeling **drowsy (sleepy)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
10. Your having a **dry mouth** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
11. Your feeling **sad** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
12. Your **vomiting** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
13. Your **numbness or tingling** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
14. Your **weakness** on one side of the body at its WORST?	○	○	○	○	○	○	○	○	○	○	○
15. Your difficulty **understanding** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
16. Your difficulty **speaking** (finding the words) at its WORST?	○	○	○	○	○	○	○	○	○	○	○

SAMPLE

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Date: ☐☐ / ☐☐ / ☐☐
(month) (day) (year)

Subject Initials: _____

MD Anderson # : ☐☐☐☐☐☐

Study Name: _____
Protocol #: _____
PI: _____

PDMS # : ☐☐☐☐

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
17. Your **seizures** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
18. Your difficulty **concentrating** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
19. Your **vision** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
20. Your change in **appearance** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
21. Your change in **bowel pattern** (diarrhea or constipation) at its WORST?	○	○	○	○	○	○	○	○	○	○	○
22. Your **irritability** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Part II. How have your symptoms interfered with your li

Symptoms frequently interfere with h[illegible] we[illegible] function. How much have your symptoms interfered with the following items in the last 2[illegible]:

SAMPLE

	Did not interfere 0	1	2	3	4	5	6	7	8	9	Interfered Completely 10
23. **General activity?**	○	○	○	○	○	○	○	○	○	○	○
24. **Mood?**	○	○	○	○	○	○	○	○	○	○	○
25. **Work (including work around the house)?**	○	○	○	○	○	○	○	○	○	○	○
26. **Relations with other people?**	○	○	○	○	○	○	○	○	○	○	○
27. **Walking?**	○	○	○	○	○	○	○	○	○	○	○
28. **Enjoyment of life?**	○	○	○	○	○	○	○	○	○	○	○

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APPENDIX 3 Sample Drug Diary

Progesterone drug diary

Patient Name: ________________________________

Key: Dose (eg 25,50,75, 100)
Time (indicate AM or PM)
Sites (R/L abd, arm, thigh)

Month: ____________Year: ___________

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
__ Dose: Time: Sites:	__ Dose: Time: Sites:	__ Dose: Time: Sites:	__ Dose: Time: Sites:	__ Dose: Time: Sites:	__ Dose: Time: Sites:	__ Dose: Time: Sites:
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APPENDIX 4 Abbreviations and definition of terms

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BBB	Blood-brain barrier
BP	Blood pressure
CI	Confidence interval
C_{max}	Maximum plasma concentration
CAPA	Corrective and Preventive Actions
CBC	Complete blood count
CMP	Complete metabolic panel
CNS	Central nervous system
CR	Complete response
CRC	Clinical research coordinator
CTCAE	Common Terminology Criteria for Adverse Event
$C_{trough,ss}$	Trough concentration at steady state
DLT	Dose limiting toxicity
DSMC	Data Safety Monitoring Committee
DSMP	Data Safety Monitoring Plan
eCRF	Electronic case report form
EOS	End of study
ERMS	Emory Research Management System
FCBP	Female of childbearing potential
FDA	Food and Drug Administration
GBM	Glioblastoma
GCP	Good Clinical Practice
H&P	History and Physical
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus

Abbreviation or special term	Explanation
HR	Hazard ratio
IB	Investigator's Brochure
ICF	Informed consent form
IDS	Investigational Drug Service
IND	Investigational New Drug
IHC	Immunohistochemistry
IM	Intramuscular
IP	Investigational product
IRB	Institutional Review Board
IV	Intravenous
KPS	Karnofsky Performance Scale
MGMT	Methylguanine methyl transferase
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
ORR	Objective response rate
OS	Overall survival
QOL	Quality of life
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PR	Partial response or Progesterone receptor
RR	Response rate
SAE	Serious adverse event
SC	Subcutaneous
SD	Stable disease
SoC	Standard of Care
SOP	Standard Operating Procedure
$T_{1/2}$	Half-life
T_{max}	Serum peak concentration time
TBD	To be determined
TMZ	Temozolomide

Abbreviation or special term	Explanation
ULN	Upper limit of normal
UP	Unanticipated problem
US	United States
WCSR	Winship Central Subject Registration