CLINICAL STUDY PROTOCOL

A Phase 1/2 Study of SL-701, a Subcutaneously Injected Multivalent Glioma-Associated Antigen Vaccine, in Adult Patients with Recurrent Glioblastoma Multiforme

Drug Name:	SL-701
Protocol Number:	**STML-701-0114**
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IND Number:	015929
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PROTOCOL APPROVAL SIGNATURE

Protocol Title: A Phase 1/2 Study of SL-701, a Subcutaneously Injected Multivalent Glioma-Associated Antigen Vaccine, in Adult Patients with Recurrent Glioblastoma Multiforme

Protocol Number: STML-701-0114

This study will be conducted in compliance with the clinical study protocol (and amendments), ICH guidelines for current Good Clinical Practice and applicable regulatory requirements. Compliance with Good Clinical Practice standards provides public assurance that the rights, safety, and well-being of study patients are protected, consistent with the principles that have their origin in the Declaration of Helsinki.

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PROTOCOL SYNOPSIS

Name of Finished Product: SL-701
Name of Active Ingredient: MPS-380 (IL-13Rα2$_{345-353:1A9V}$), MPS-381 (EphA2$_{883-891}$), MPS-481 (Survivin$_{95-104:3M}$), and MPS-199 (Tet$_{A830}$) peptides
Study Title: A Phase 1/2 Study of SL-701, a Subcutaneously Injected Multivalent Glioma-Associated Antigen Vaccine, in Adult Patients with Recurrent Glioblastoma Multiforme
Study Number: STML-701-0114
Study Phase: 1/2
Primary Objectives: The primary objectives are to: • Characterize the safety and tolerability of SL-701 and SL-701 in combination with bevacizumab. • Estimate the percent of patients alive 12 months after the initiation of SL-701 (OS-12). • Estimate the objective response rate (ORR).
Secondary Objectives: The secondary objectives are to: • Estimate the duration of response (DR). • Estimate the percent of patients alive and progression-free survival at 6 months (PFS-6) after the initiation of SL-701. • Estimate the distributions of progression-free survival (PFS) and overall survival (OS).
Exploratory Objectives: The exploratory objectives are to: • Estimate the relationships between measures of immunogenicity and anti-tumor efficacy. • Evaluate available post-vaccine tumor tissue for glioma-associated antigen (GAA) expression status and infiltration of GAA-specific T-cells.
Study Population: Approximately 76 adult patients with recurrent glioblastoma multiforme (GBM), 46 in Stage 1 and 30 in Stage 2. At least 56 of the 76 treated patients must have measureable disease based on contrast enhanced magnetic resonance imaging (MRI) or computed tomography (CT) scans.

Study Design:

This is a multicenter, open label phase 1/2 study evaluating the efficacy and safety of SL-701 as a treatment for recurrent GBM, divided into 2 stages. Approximately 76 patients will be treated in the study, 46 in Stage 1 and 30 in Stage 2; at least 56 of these patients must have measureable disease. During Stage 1, patients will receive SL-701 with the vaccine adjuvants granulocyte macrophage-colony stimulating factor (GM-CSF) injection and imiquimod topical cream. The first 24 patients treated in Stage 1 will be subject to the toxicity monitoring rules (Section 3.2.1). During Stage 2, patients will receive SL-701 with the vaccine adjuvant poly-ICLC and bevacizumab.

To be eligible, patients must have shown unequivocal evidence of a first tumor recurrence or progression on the initial treatment regimen (prior to enrollment in this study) by MRI or CT as in the inclusion criteria, which should be performed within 14 days prior to start of SL-701 (see **Inclusion Criteria** for details). Subsequent tumor response assessments will be performed every 8 weeks thereafter until the Investigator determines there is evidence of progressive disease (PD) using objective response criteria. Patients who are evaluable for objective response will also be followed for duration of response, and all treated patients will be followed for OS and PFS until assessment of the primary objectives is completed.

Study Centers:

Up to 30 sites in North America.

Inclusion Criteria:

1. 18 years of age or older.
2. Histologically confirmed GBM or World Health Organization (WHO) Grade IV variants (gliosarcoma, glioblastoma with oligodendroglial features, or giant cell glioblastoma).
3. Unequivocal evidence of a first tumor recurrence or progression on the initial treatment regimen (prior to enrollment on this study), consisting of surgical intervention (biopsy and/or resection), radiation, and temozolomide chemotherapy, as assessed by MRI or CT scan of the brain with and without contrast within 14 days prior to the start of SL-701. If receiving corticosteroids, the dose must be stable or decreasing for at least 5 days prior to the scan. Patients unable to undergo MRI because of non-compatible devices can be enrolled, provided CT scans are obtained and are of sufficient quality. Patients without non-compatible devices may not have CT scans performed to meet this requirement. For each patient, the same imaging technique should be performed throughout the study, for purposes of assessing tumor response or PD.
4. For patients who have undergone resection of recurrent or progressive tumor prior to study enrollment, the following conditions must apply:
    - Recovery from the effects of surgery.
    - Residual disease following resection of recurrent tumor is not mandated for eligibility into the study. To best assess the extent of residual disease post-operatively, an MRI should be performed:
        - No later than 96 hours (h) in the immediate post-operative period; or
        - At least 4 weeks post-craniotomy (7 days for stereotactic biopsy), within 14 days prior to the start of SL-701, and on a corticosteroid dosage that has been stable or

decreasing for at least 5 days.

5. Patients who have not had resection of recurrent or progressive disease must have measurable disease.
6. At least 56 of the approximately 76 patients treated must have measurable disease, defined as at least one, contrast-enhancing lesion measuring at least 1 cm in 2 planes (axial, coronal, or sagittal).
7. No evidence of hemorrhage on the baseline MRI or CT scan other than those that are ≤Grade 1 and either post-operative or stable on at least 2 consecutive scans.
8. Recovery from prior therapy toxicity, defined as resolution of all treatment-related adverse events (AEs) to ≤Grade 1 or pre-treatment baseline (except alopecia and lymphopenia).
9. At least 12 weeks from prior radiotherapy to the start of SL-701 unless there is new enhancement outside of the radiation field or unequivocal histopathologic evidence of recurrent tumor subsequent to radiotherapy.
10. No chemotherapy or investigational agent for at least 3 weeks prior to the start of SL-701.
11. Human leukocyte antigen (HLA)-A2 positive.
12. A tumor tissue sample is provided for immunohistochemical analysis of relevant antigens, immune markers and potential prognostic factors. Preferably a paraffin block or 10-12 unstained slides will be submitted prior to study entry. Patients for whom tumor samples are unavailable or inadequate are permitted to participate in the study; however, the absence of available/adequate tumor specimen must be documented.
13. Karnofsky performance status (KPS) score ≥70%.
14. Adequate organ function, including the following:
    - Absolute neutrophil count (ANC) ≥1,000/μL, platelets ≥100,000/μL.
    - Serum creatinine ≤1.5 × the upper limit of normal (ULN).
    - Bilirubin ≤1.5 × ULN.
    - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 × ULN.
15. Women of childbearing potential must have a negative serum or urine pregnancy test within 3 days prior to the start of SL-701 treatment.
16. Female patients of childbearing potential and sexually active male patients must agree to use an acceptable form of contraception for heterosexual activity (ie, oral contraceptives, double-barrier methods, hormonal injectable, transdermal, or implanted contraceptives, tubal ligation, or vasectomy of their sexual partner(s) for >40 days before Screening, during the study, and for 60 days after the last dose of study drug. Men should not donate semen during the study and for 60 days after the last dose of study drug.
17. Female patients without childbearing potential (spontaneous amenorrhea for >12 months or surgically sterilized by tubal ligation, hysterectomy, or bilateral oophorectomy >6 months before Screening) are eligible for inclusion without contraceptive use restriction.
18. Able and willing to comply with protocol requirements, in the opinion of the Investigator.
19. A written and voluntarily signed informed consent must be obtained from the patient or legally authorized representative, in accordance with local regulations, before the initiation of any

study-related procedures. The patient or legally authorized representative must be able to read and understand the informed consent form (ICF).

Exclusion Criteria:

1. Prior cancer chemotherapy, bevacizumab (or other vascular endothelial growth factor [VEGF]/VEGF receptor [VEGFR]-directed agent), or an investigational agent for recurrent/progressive GBM or prior bevacizumab as part of initial therapy (prior chemotherapy or investigational agents are permitted as part of initial therapy; VEGF/VEGFR-directed agents are not permitted).
2. Contrast-enhancing tumor that is any of the following:
   - Multi-focal (defined as 2 separate areas of contrast enhancement measuring at least 1cm in 2 planes that are not contiguous on either fluid-attenuated inversion recovery [FLAIR] or T2 sequences);
   - Associated with either diffuse subependymal or leptomeningeal dissemination; or
   - 4 cm in any dimension.
3. Requirement of systemic corticosteroid therapy >4 mg/day of dexamethasone or equivalent or requirement of increasing dose of systemic corticosteroids during the 7 days prior to the start of SL-701 treatment.
4. Surgical resection or major surgical procedure within 4 weeks prior to the start of SL-701, or stereotactic biopsy within 7 days prior to the start of SL-701.
5. Radiation therapy, local therapy (except for surgical re-resection), or systemic therapy following first recurrence/progressive disease. Excluded local therapies following first recurrence/progressive disease include stereotactic radiation boost, implantation of carmustine biodegradable wafers (Gliadel), intratumoral or convection-enhanced delivery administered agents, etc.
6. Active infection requiring intravenous (IV) antibiotics.
7. History of cancer (other than GBM) within the past 2 years that has substantial metastatic or local recurrence potential and could negatively impact survival and/or potentially confound tumor response assessments within this study.
8. Clinically significant cardiovascular disease (eg, uncontrolled or any New York Heart Association Class 3 or 4 congestive heart failure, uncontrolled angina, history of myocardial infarction or stroke within 6 months of study entry, uncontrolled hypertension or clinically significant arrhythmias not controlled by medication).
9. Known immunosuppressive disease or active systemic autoimmune disease (such as systemic lupus erythematosus), human immunodeficiency virus infection, active or chronic Hepatitis B or Hepatitis C, or has taken an immunosuppressive agent within 4 weeks prior to the start of SL-701 treatment. Patients with vitiligo, type 1 diabetes mellitus, hypothyroidism due to autoimmune condition only requiring hormone replacement therapy, psoriasis not requiring systemic therapy, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
10. Any condition that in the Investigator's opinion makes the patient unsuitable for study participation.

11. Requires therapeutic anticoagulation with warfarin at baseline; patients must be off warfarin or warfarin-derivative anti-coagulants for at least 7 days prior to starting study drug; however, therapeutic or prophylactic therapy with low-molecular weight heparin is allowed.
12. Has history of known coagulopathy that increases risk of bleeding or a history of clinically significant hemorrhage within 12 months of start of study drug.
13. Has evidence of intratumoral or peritumoral hemorrhage on baseline MRI scan other than those that are ≤Grade 1 and either post-operative or stable on at least 2 consecutive MRI scans
14. Has gastrointestinal bleeding or any other hemorrhage/bleeding event National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) >Grade 3 within 6 months of start of study drug.

Investigational Product, Dose, and Mode of Administration:

SL-701 consists of HLA-A2 restricted epitope peptides, MPS-380 (IL-13Rα2$_{345-353:1A9V}$), MPS-381 (EphA2$_{883-891}$), and MPS-486 (Survivin$_{95-104:3M}$), derived from 3 antigens that are overexpressed by glioma relative to normal tissues. SL-701 also includes MPS-199, a peptide that functions as a helper T-cell epitope derived from the Tetanus Toxoid, Tet$_{A830}$. SL-701 peptides are designed to activate and expand the population of cytotoxic T-cells (CD8+ T-cells) that are specific for these glioma epitopes, leading to their migration into the brain and killing of glioma cells.

In Stage 1, a complete dose of study drug consists of the administration of a sequence of 3 agents, SL-701 emulsion (SL-701 in Montanide®) subcutaneous (SC) injection, GM-CSF SC injection, and imiquimod topical cream, within an approximate 5-minute time frame. Topical application of imiquimod cream at the injection site is repeated at 24 hours (h) after each SL-701 emulsion injection.

In Stage 1, patients will be treated with SL-701 emulsion every 14 days initially for 12 doses, followed by administration every 28 days until PD, withdrawal of informed consent, unacceptable toxicity, or non-compliance. Administration parameters for SL-701 emulsion, GM-CSF, and imiquimod are summarized in the table below.

In Stage 2, a complete dose of investigational treatment consists of the administration of a sequence of 2 agents, SL-701 emulsion injection, and poly-ICLC intramuscular (IM) injection, within an approximate 20-minute time frame. Patients will also receive IV bevacizumab. SL-701 emulsion and the adjuvant poly-ICLC will be administered twice weekly for the initial 2 weeks, every 7 days during the subsequent 3 doses, and subsequently every 14 days for the subsequent 9 doses (16 doses total) through Week 22, and every 4 weeks thereafter. Bevacizumab will be administered every 2 weeks, subsequent to the administration of SL-701/poly-ICLC. Administration parameters for SL-701, poly-ICLC and bevacizumab are summarized in the table that follows.

Agent and Dose	Preparation and Route of Administration	Schedule
SL-701 in Montanide®; 1.0 mL injection taken from 0.7 mL of SL-701 mixed at a 1:1 (v/v) ratio with 0.7 mL of Montanide[1]	Preferred site of SC injection is in the right or left upper arms with intact draining axillary nodes, alternating locations between individual vaccination dates. In case participants do not possess intact axillary lymph nodes as the draining nodes, administration is in the upper thigh on the same side with intact inguinal lymph nodes. The injection site should be selected and the area cleaned with soap and water and then dried thoroughly for at least 10 minutes. A circle with a radius of 18 mm will be marked out with ink at the injection site prior to SC injection to serve as a guide for the GM-CSF injection and imiquimod application.	Stage 1: Day 1; Weeks 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 22, then every 4 weeks thereafter. Stage 2: Days 1, 4, 8 (Week 1), and 11; Weeks 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 22, then every 4 weeks thereafter,
Stage 1 only: GM-CSF 150 µg	GM-CSF should be administered as a SC injection immediately after SL-701 emulsion administration and within 1 cm from the center of the SL-701 emulsion injection site, prior to application of topical imiquimod.	Day of each SL-701 emulsion dose,
Stage 1 only: Imiquimod Cream, 5% supplied in 250 mg single-use packets	Immediately (within 5 minutes) following the administration of the SL-701 emulsion, approximately one-half packet (125 mg) of imiquimod cream will be applied topically on the injection site. Study site personnel and patients will be instructed to wash hands before and after imiquimod topical use. Patients will be provided with instructions for the application process for the imiquimod cream at 24 h at the SL-701 emulsion injection site and told not to wash the area for 48 h after the SL-701 emulsion injection (24 h after the second imiquimod application).[2] The imiquimod cream should be rubbed in until the cream is no longer visible.	Day of each SL-701 emulsion dose and 24 h after each SL-701 emulsion dose.
Stage 2 only: Poly-ICLC 1.6mg (1,600 µg)	Within 20 minutes following the administration of the SL-701 emulsion, poly-ICLC should be administered as an IM injection in the same extremity as was administered the SL-701 (deltoid muscle, unless contraindicated).	Day of each SL-701 emulsion dose.
Stage 2 only: Bevacizumab Solution for injection	In Stage 2, following the administration of SL-701 and poly-ICLC, bevacizumab will be administered IV at a dose of 10 mg/kg. Bevacizumab infusions may occur over 30, 60, or 90 minutes in accordance with institutional practices and guidelines.	Day 1; Weeks 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 22, then every 2 weeks thereafter.

[1]A 1.0 mL dose of the emulsion contains 0.3 mg each of the MPS-380, MPS-381, and MPS-486 peptides and 0.2 mg of the MPS-199 peptide.
[2]In situations where the 24h topical imiquimod is not administered according to protocol schedule for reasons other than adverse events (ie, the patient forgets to apply at 24 h), the patient may apply imiquimod during an additional 24-hour period subsequent to the stipulated administration time. Subsequent to this 24-hour window, the imiquimod dose will be considered "missed" and should not be applied.

The primary assessment of response will be based on modified Radiologic Assessment in Neuro-Oncology (RANO) criteria (Wen 2010). The presence of any of the following will define PD:

- ≥25% increase in the bidimensional product of enhancing tumor compared to pre-SL-701 baseline or best response following initiation of SL-701 (unidimensional increases in contrast-enhancing tumor ≤1cm will not result in discontinuation of investigational therapy, unless there

is additional clinical/radiographic evidence of unequivocal GBM progression);

- New measureable contrast-enhancing lesion(s) defined as lesion(s) that are at least 1 cm in at least 2 planes; or
- Significant clinical decline not attributable to co-morbid event or change in concurrently administered medication.

As part of each tumor response assessment using modified RANO criteria, information will be collected on the patient's clinical status (eg, stable, improved, or declining since the last assessment), functional neurological status using the KPS score, and concomitant medications, including corticosteroid use. A patient with radiographic evidence of PD after initiating SL-701 may continue study drug for an additional 8 weeks, provided that the patient does not experience significant clinical deterioration and/or significant toxicity, as determined by the treating Investigator and Sponsor. If follow-up imaging after 8 weeks of additional study drug confirms PD as defined above, study drug will be discontinued due to PD. Unidimensional increases in contrast-enhancing tumor ≤1cm will not result in discontinuation of investigational therapy, unless there is additional clinical/radiographic evidence of unequivocal GBM progression. Follow-up imaging may be performed <8 weeks after the initial detection of PD (eg, after 4 weeks) if medically appropriate. If PD is confirmed on follow-up imaging at 2 consecutive time points ≥4 weeks apart, the PD date is the date that PD criteria were initially met.

Concomitant Medications:

Allowed Medications/Therapies:

Concomitant systemic corticosteroids are to be avoided if medically feasible. If used, corticosteroid doses should be the minimum necessary for appropriate clinical management. Any patient requiring initiation or significant increase in corticosteroid dosing due to progressive neurologic signs or symptoms should undergo a rigorous evaluation for recurrent GBM. Efforts should be made to taper off corticosteroids as quickly as possible in the absence of PD. Topical steroids may be used only for severe injection site reactions. Inhaled corticosteroids may be administered as needed. As appropriate, topical or systemic non-steroidal anti-inflammatory agents or antihistamines may be used as alternatives. Patients with a history of prior Hepatitis B infection with evidence of immunity (ie, positive HBV surface antibody [HBsAb]) should be treated with appropriate anti-viral therapy (ie, lamivudine, adefovir, or similar anti-viral agents) for the duration of investigational therapy.

***Prohibited Medications/Therapies*:**

Therapies including investigational agents administered primarily for anti-tumor intent, such as prior chemotherapy, bevacizumab (or other VEGF/VEGFR-directed agent), or an investigational agent for recurrent/progressive GBM or prior bevacizumab as part of initial GBM therapy.

Toxicity Monitoring Rules:

The toxicity monitoring rules for the following events will be applied to the first 24 patients treated in the study. Given the possibly long latency period for the toxicities of interest, there will not be any interruption in accrual to assess these events.

***Regimen Limiting Toxicity*:**

A regimen-limiting toxicity (RLT) includes any of the following events that occur anytime through the first 12 doses of study drug (ie, from first dose through approximately 24 weeks) which are considered possibly, probably or definitely related to investigational therapy:

- ≥Grade 3 bronchospasm or Grade 2 bronchospasm that does not resolve within 24 hours despite appropriate medical therapy (ie, inhaled albuterol);
- ≥Grade 3 generalized urticaria;
- Other ≥Grade 3 allergic reaction, such as exfoliative erythroderma, anaphylaxis, or vascular collapse;
- ≥Grade 3 non-hematologic toxicity (excluding hepatic laboratory toxicity and excluding Grade 3 hypertension in which blood pressure resolves to <160 [systolic] and <100 [diastolic] with intensified antihypertensive therapy) related to the study drug regimen including ≥Grade 3 injection site reaction due to SL-701 emulsion or immunoadjuvant administration, with the exception of transient Grade ≥ 3 events as detailed below;
- Intolerable ≥Grade 3 skin (injection site) reaction lasting ≥7 days (at ≥Grade 3) or that recurs despite discontinuation of imiquimod, if applicable;
- ≥Grade 3 constitutional symptoms (including fatigue, fever, malaise, myalgia, edema [non-cerebral]) that persist for >48 h and that recur and persist for >48 h despite discontinuation of imiquimod, if applicable;
- ≥Grade 3 nausea/vomiting or diarrhea exceeding 24 h despite sufficient anti-emetic or anti-diarrheal therapy, respectively;
- Grade 3 or 4 neutropenia with fever;
- Grade 4 hematologic toxicity (cytopenia) lasting >5 days;
- Cerebral edema associated with severe clinical manifestations (Grade 4), which in the Investigator's opinion is related to study therapy. Cerebral edema (Grade 4) due to underlying tumor progression (based on imaging), change in concurrent medications (such as rapid decrease in corticosteroids), or a co-morbid event (such as status epilepticus, severe electrolyte imbalance) as well as <Grade 4 cerebral edema will not be classified as RLT. Examples of this RLT include severe manifestations attributed to pseudoprogression that do not improve with medical or surgical intervention.

A review will take place following each RLT. Additionally, if a RLT occurs in ≥2 of the first 3 patients, ≥3 of the first 6 patients, ≥4 of the first 9 patients, ≥4 of the first 12 patients, ≥5 of the first 15 patients, ≥6 of the first 18 patients, or ≥7 of the first 24 patients, accrual will be suspended and the Investigator, Medical Monitor and Sponsor will make decisions regarding continuation of study accrual.

Events meeting the above criteria which occur subsequent to the first 12 doses of study drug (ie, more than approximately 24 weeks following the start of investigational therapy) will be considered RLT-level events. Evaluation of safety data for RLT-level events will occur according to similar guidelines/parameters as defined above (for RLTs).

***Sudden or Unexpected Deaths Related to SL-701*:**

A safety review will take place following each sudden or unexpected death that is not considered by the Investigator to be disease-related and is considered to be related to SL-701. Additionally, if such an event occurs in ≥2 of the first 3 patients, ≥3 of the first 6 patients, ≥4 of the first 9 patients, ≥4 of the first 12 patients, ≥5 of the first 15 patients, ≥6 of the first 18 patients, or ≥7 of the first 24 patients, accrual will be suspended and the Investigator, Medical Monitor and Sponsor will make decisions

regarding the continuation of study accrual; (Note: these are general guidelines, and lower rates of treatment-related deaths would likely result in study discontinuation).

In addition to the toxicity monitoring described above, an Independent Data Monitoring Committee (IDMC) will be established prior to the inclusion of the first patient in the study. The IDMC will evaluate all available safety data when 10 patients have received at least 2 doses of SL-701, died, or withdrawn from the study. The IDMC will also monitor for RLTs throughout the study (ie, beyond the first 24 treated patients) to confirm the risk of RLTs is <33%, and the Committee may recommend interruption of accrual at any time during the study if excessive toxicity is observed. Details regarding the content and timing of these safety reviews will be provided in the IDMC Charter.

During Stage 2, the IDMC will also evaluate available safety data when 10 patients have received at least 3 doses of SL-701 (and adjvuant) and bevacizumab, died, or are withdrawn from the study.

Assessments:

Efficacy Assessments:

Efficacy assessments include ORR, duration of response, OS-12, PFS-6, OS, and PFS. Tumor response will be assessed using modified RANO criteria. For comparative purposes, response will also be assessed by the Response Evaluation Criteria in Solid Tumors (RECIST) (version 1.1) (Eisenhauer 2009). MRI scans for assessment of ORR will be obtained during the Screening period and then every 8 weeks after the first dose of SL-701. Clinical assessment for PD will be made at every visit, both visits when only scans are performed and when SL-701 is administered (Day 1, every 2 weeks thereafter through Week 26, then approximately every 4 weeks (28 days) after Week 26).

ORR is defined as the proportion of patients achieving a best response of complete response (CR) or partial response (PR) on 2 consecutive MRIs obtained ≥4 weeks apart. DR is defined as the time from the date measurement criteria are first met for objective response until the first date that the criteria for PD is met, or death due to any cause, whichever occurs first.

OS-12 is defined as the percentage of patients alive 12 months (52 weeks) after the initiation of SL-701 (in an additional secondary analysis, OS-12 will be evaluated by Kaplan-Meier estimate). OS is defined as the time from the date of initiation of SL-701 to the date of death from any cause. PFS-6 is defined as the percentage of patients alive and progression-free at 6 months (26 weeks) after the initiation of SL-701 (PFS-6 will also be evaluated by Kaplan-Meier estimate). PFS is defined as the time from the date of initiation of SL-701 to the date of PD or death from any cause, whichever occurs first.

***Safety Assessments*:**

Safety assessments include AEs, serious adverse events (SAEs), physical examinations, vital sign and weight measurements, clinical laboratory evaluations, and reasons for treatment discontinuation due to toxicity. Progression of disease and disease-related death will not be considered AEs or SAEs. The severity of AEs will be assessed using the NCI CTCAE, Version 4.03 (or higher).

The AE reporting period for each patient enrolled in the study begins from the time the patient signs the ICF and is continuous through 30 days after the last dose of study drug. All AEs that occur in enrolled patients during the adverse reporting period specified in the protocol must be collected in the study database and reported to INC Research, whether or not the event is considered related to study drug treatment. Any known untoward event that occurs beyond the AE reporting period that the Investigator assesses as related to study drug treatment should also be reported as an AE.

***Immunological Monitoring Studies*:**

Blood samples (6 × 10 cc green top tubes) will be collected on Day 1, at Weeks 4, 8, 12, 16, and 24, and then every 8 weeks thereafter (approximately) to evaluate the magnitude of immune response in peripheral blood mononuclear cells (PBMC) against the targeted GAA peptides using IFN-γ-enzyme-linked immuno-spot (ELISPOT) assay and flow cytometric analyses of lymphocyte activation. All patient samples will be collected at the respective treatment sites and promptly shipped to a single central processing laboratory to minimize variability.

Tumor tissue samples, whenever there is available pretreatment tissue or tumor is biopsied for any reason throughout the duration of the study, will be archived and assessed for GAA expression status and infiltration of GAA-specific T-cells.

Statistical Methods:

***Sample Size*:**

The initially planned sample size of 100 patients was based on the following assumptions for the co-primary endpoints of OS-12 and ORR (Wick 2010, van den Brent 2009, Batchelor 2013):

OS-12:

- The null hypothesis is that OS-12 for patients treated with SL-701 is ≤25%;
- The alternative hypothesis is that OS-12 for patients treated with SL-701 is ≥40%;
- Testing will be by an exact one-sample binomial superiority test with type I error rate of 1.25%, 1-sided.

ORR (by modified RANO criteria):

- The null hypothesis is that ORR for patients treated with SL-701 is ≤10%;
- The alternative hypothesis is that ORR for patients treated with SL-701 is ≥25%;
- Testing will be by an exact one-sample binomial superiority test with type I error rate of 1.25%, one-sided;
- At least 80 patients will be evaluable for ORR.

Based on these assumptions, the power for the initially planned sample size was approximately 82% for OS-12 and 92% for ORR. Accrual to Stage 1 one of the study was discontinued following the accrual 46 patients (all evaluable for ORR) who received SL-701 emulsion, GM-CSF, and imiquimod. Consequently the power for Stage 1 given the actual enrollment was approximately 48% for OS-12 and 62% for ORR.

In Stage 2, the null and alternative hypotheses for OS-12 will remain the same as those indicated above. The null and alternative hypotheses for ORR will be ≤40% and ≥60%, respectively. All testing in Stage 2 will be at a type I error rate of 5%, one-sided. If 30 patients (assumed all evaluable for ORR) are enrolled in Stage 2 (SL-701 with adjuvant poly-ICLC and with bevacizumab) the power is approximately 71% for OS-12 and 55% for ORR.

***Analysis Conventions*:**

Demographic (eg, gender, age, race, ethnicity) and baseline characteristics (eg, KPS, height, weight, and prior therapy) will be summarized with descriptive statistics.

All enrolled patients who received any amount of study drug will be included in the safety analyses. Treatment-emergent AEs through 30 days after last dose of study drug will be summarized by Medical

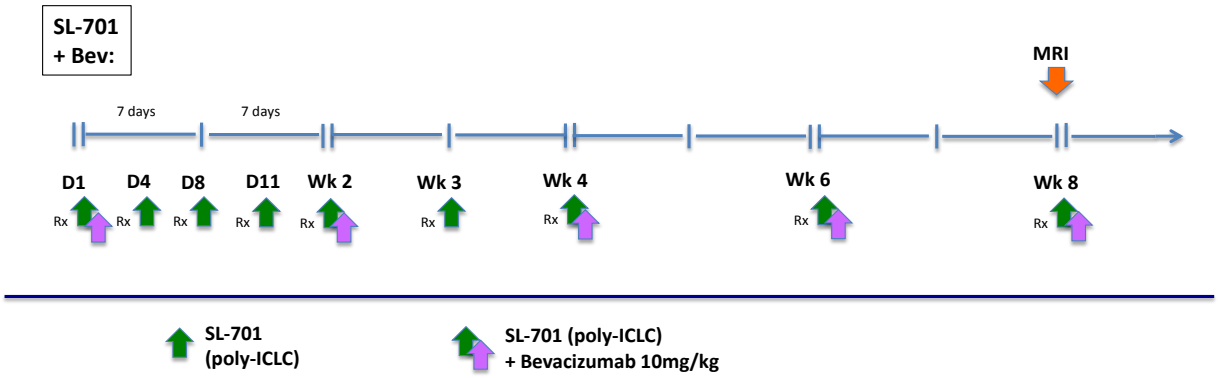
Dictionary for Regulatory Activities (MedDRA™), Version 13.1 (or higher), system organ class and preferred term. The incidences and percentages of patients experiencing each AE preferred term will be summarized with descriptive statistics. The severity of AEs will also be summarized by NCI CTCAE, Version 4.03 (or higher), grade and by causality (relationship to study drug). Grade 3 and 4 AEs, SAEs, and AEs leading to withdrawal, dose modification, or treatment discontinuation will also be summarized by preferred term.

Laboratory results will be classified according to NCI CTCAE, Version 4.03 (or higher). Laboratory results not corresponding to an NCI CTCAE term will not be graded. Incidences of laboratory abnormalities will be summarized with descriptive statistics.

Vital signs and physical examination results will be summarized with descriptive statistics.

Testing for the co-primary endpoints will be by exact one-sample binomial tests with type I error rate of 1.25%, 1-sided for Stage 1 of the study and 5%, 1-sided for Stage 2 of the study. Exact 2-sided 97.5% (Stage 1) or 90% (Stage 2) confidence intervals will be calculated for OS-12, ORR, and PFS-6. Distributions for DR, OS, and PFS will be estimated by Kaplan-Meier methodology.

The treatment schedule for Stage 2 is depicted below:



ABBREVIATIONS

Abbreviation	Term
AA	anaplastic astrocytoma
AE	adverse event
AG	anaplastic glioma
AK	Actinic keratosis
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AO	anaplastic oligodendroglioma
AOA	anaplastic oligoastrocytoma
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BSG	brain stem glioma
CFR	Code of Federal Regulations
CI	confidence interval
CNS	central nervous system
CR	complete response
CRO	contract research organization
CRO	contract research organization
CSC	cancer stem cell
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTL	cytotoxic T lymphocyte
DC	dendritic cell
DIPG	diffuse intrinsic pontine glioma
DR	duration of response
dsRNA	double-stranded RNA
EAE	Experimental autoimmune encephalomyelitis
eCRF	electronic case report form
EGFRvIII	epidermal growth factor receptor variant III

Abbreviation	Term
EGW	external genital warts
ELISPOT	enzyme-linked immunosorbent spot
EMA	European Medicines Agency
EphA2	ephrin type-A receptor 2
FAS	full analysis set
FDA	Food and Drug Administration
FLAIR	fluid-attenuated inversion recovery
GAA	glioma-associated antigen
GBM	glioblastoma multiforme
GM-CSF	granulocyte macrophage-colony stimulating factor
h	hour(s)
HBsAb	hepatitis B surface antibody
HGG	high-grade glioma
HLA	human leukocyte antigen
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFN-γ	interferon-gamma
IL	Interleukin
IL-13Rα2	interleukin -13 receptor alpha 2 protein chain
IM	Intramuscular
IND	Investigational New Drug application
INR	international normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	Intravenous
KPS	Karnofsky performance status
LGG	low-grade glioma
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Term
MHC	major histocompatibility complex
mmHg	millimeter(s) of mercury
MRI	magnetic resonance imaging
N	number of patients with an observation
N	number of patients in the dataset or population
NBSG	non-brain stem glioma
NCI CTCAE	National Cancer Institute Common Terminology for Adverse Events
ORE	objective response evaluable
ORR	objective response rate
OS	overall survival
OS-12	percent of patients alive 12 months after the initiation of SL-701
PBMC	peripheral blood mononuclear cells
PD	progressive disease
PFS	progression-free survival
PFS-6	percent of patients alive and PFS
poly-ICLC	polyinosinic-polycytidylic acid stabilized with polylysine and carboxymethyl cellulose
PR	partial response
PS	performance status
PT	preferred term
RANO	Response Assessment in Neuro-Oncology
RECIST	Response Evaluation Criteria in Solid Tumors
rhu-GM-CSF	recombinant human granulocyte-macrophage colony stimulating factor
RLT	regimen limiting toxicity
RNA	ribonucleic acid
RT	Radiotherapy
SAE	serious adverse event
sBCC	superficial basal cell carcinoma
SC	Subcutaneous
SD	Stable disease

Abbreviation	Term
SOC	system organ class
TAA	tumor-associated antigen
TEAE	treatment-emergent adverse event
TLR	toll-like receptor
TMZ	Temozolomide
TT	tetanus toxoid
ULN	upper limit of normal
US	United States
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
WHO	World Health Organization

1. INTRODUCTION AND STUDY RATIONALE

1.1 Glioma Background

1.1.1 Description and Characterization

Glioma, which arises from glial cells, comprises approximately 30% of all primary brain and central nervous system (CNS) tumors and 80% of all malignant brain tumors. Glioma is classified by cell type and grade, as determined by the pathological evaluation of the tumor and its location. The main type of glioma, by cell type, is astrocytoma, of which glioblastoma multiforme (GBM) is the most common. Of numerous grading systems currently in use, the most common is the World Health Organization (WHO) system for astrocytoma under which tumors are graded from I (least advanced disease and best prognosis) to IV (most advanced disease and worst prognosis):

- Low-grade [WHO Grade II] gliomas (ie, LGG) are well-differentiated, tend to exhibit benign characteristics and portend a better prognosis. However, they have considerable rates of recurrence and of transformation to high-grade gliomas (HGG) over time and should be classified as malignant.
- High-grade [WHO Grade III–IV] gliomas (ie, HGG) are undifferentiated or anaplastic. These include anaplastic astrocytomas (Grade III) and GBM (Grade IV), which is frequently also referred to as glioblastoma. Most malignant gliomas are HGGs, which are very aggressive, difficult to treat, and carry a poor prognosis.

Glioblastoma (ie, GBM), the most common HGG in adults and primary malignant central nervous system tumor, is diagnosed in approximately 11,000 individuals in the United States (US) each year.

1.1.2 Treatment

Despite advances in therapeutic strategies, including surgical resection, radiotherapy, chemotherapy, and targeted agents, the prognosis for patients with GBM is poor. A multi-component treatment strategy combining surgical resection, radiotherapy (RT), and temozolomide (TMZ) chemotherapy is considered the standard initial (ie, first-line) treatment in adults with newly diagnosed GBM disease.

Bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor (VEGF), received accelerated approval by the Food and Drug Administration (FDA) for recurrent GBM based on an objective response rate (ORR) of approximately 20-25% (Avastin Package Insert 5/2015). Nonetheless, all patients ultimately progress on bevacizumab therapy and rapidly succumb to fulminant tumor growth due to lack of effective therapies (Norden 2008; Quant 2009). Bevacizumab has not been shown to confer prolonged overall survival in GBM, either when incorporated into initial multimodality regimens, or in recurrent settings (Chinot 2014). It has also been postulated, albeit not proven in randomized clinical studies, that cessation of anti-VEGF therapy results in rebound edema and clinical deterioration known as the so-called flare response (Chamberlain 2011). Bevacizumab has been associated with progression-free survival (PFS) and likely symptomatic benefits; recent investigation suggests that the magnitude of this benefit is comparable, whether bevacizumab is administered as part of initial therapy, at time of GBM recurrence, or at a subsequent progression (Piccioni 2014).

The overall poor response of GBM to conventional cytotoxic and more recent biologically-based therapies, is attributed to several factors, including limited delivery through the blood-brain-barrier,

inherent biologic complexity and redundancy, high-rates of intrinsic and acquired resistance to therapy, and inter-as well as intra-tumoral heterogeneity (Reardon 2006; Wen 2008).

The lack of effective treatment options for adult GBM patients has been a motivation for the development of alternative therapies, including immunotherapies. This includes specific T-cell epitope-based vaccines, which are under development as a potentially safer approach than whole glioma cell-based vaccines.

1.1.3 Survival

Outcome for adults with GBM is dismal, with a median overall survival (OS) of 16 months for newly diagnosed patients despite aggressive multi-modality therapy including surgical resection, RT, and TMZ chemotherapy. Following progressive disease (PD), salvage therapies have historically been inactive, with recent meta-analyses of Phase 2 studies conducted by the North America Brain Tumor Consortium and the North Central Cancer Treatment Group indicating rates of 6-month progression-free survival (PFS-6) and overall radiographic response of less than 10% (Ballman 2007, Wu 2010, Lamborn 2008, Gorlia 2012).

In view of these discouraging results with both traditional nonspecific cytotoxic and targeted therapeutics in malignant glioma, there is interest in developing vaccines that target antigens in order to enable the immune system to target specific antigens that are overexpressed on human brain cancer and distinguish tumor cells from surrounding normal cells, such as vaccine strategies targeting glioma-associated antigens (GAAs).

1.2 SL-701

1.2.1 Product Description

During the past decade, Hideho Okada, MD, PhD and colleagues at the University of Pittsburgh have conducted numerous preclinical and clinical studies to assess safety and optimize the immunological efficacy of a multi-peptide epitope vaccine strategy for treatment of adults and children with HGG or LGG. Five clinical studies, summarized in Section 1.3, have been conducted under investigator-sponsored investigational new drug applications (INDs) assessing different multi-peptide combinations and methods of administration. Each study included peptides derived from interleukin (IL)-13 receptor alpha 2 protein chain (IL-13Rα2) and ephrin type-A receptor 2 (EphA2) antigens, which are highly immunogenic and expressed on the cell surface of both HGG and LGG.

Stemline Therapeutics Inc. (Stemline) has licensed the exclusive worldwide rights to a clinically active oncology vaccine directed to multiple defined targets on tumor bulk and cancer stem cells (CSCs) from the University of Pittsburgh. The vaccine targets multiple defined epitopes present on the CSCs and tumor bulk of glioma, particularly GBM. The Stemline vaccine, designated SL-701, consists of human leukocyte antigen (HLA)-A2 restricted peptides that are derived from CD8+ T cell epitopes from 3 distinct antigens overexpressed by glioma cells: MPS-380 (IL-13Rα2$_{345\text{-}353:1A9V}$), MPS-381 (EphA2$_{883\text{-}891}$), and MPS-486 (Survivin$_{95\text{-}104:3M}$). MPS-380 and MPS-381 are 9 amino acids in length, and MPS-486 is 10 amino acids in length. SL-701 also includes MPS-199, a peptide that functions as a helper T cell epitope derived from Tetanus Toxoid (TT), Tet$_{A830}$, that is 16 amino acids in length.

The SL-701 vaccine is nearly identical to the GAA/TT peptide vaccine used in the University of Pittsburgh Study PRO08030085, described in Section 1.3, and both are emulsified in Montanide® ISA 51 (GAA/TT vaccines). The only difference, necessitated by the fact that the 9-mer Survivin peptide

used previously is not available for clinical development and commercialization, is that the Survivin constituent in SL-701 is a 10-mer peptide. The 10-mer Survivin peptide in SL-701 has an identical sequence as the previously used 9-mer peptide, but contains one additional amino acid. Both the 9-mer and 10-mer Survivin peptides have been shown to activate HLA-A2 restricted $CD8^+$ T cells. Moreover, each peptide has shown similar HLA binding and immunogenicity as demonstrated by peptide binding, interferon -gamma (IFN-γ) enzyme-linked immunosorbent spot (ELISPOT), and cytotoxic T lymphocyte (CTL) assays, respectively.

The toll-like receptor (TLR)-3 ligand poly-ICLC (polyinosinic-polycytidylic acid stabilized with poly-lysine and carboxymethyl cellulose) administered intramuscularly (IM) was utilized as an immunostimulatory adjuvant in 4 of the 5 initial clinical studies of the GAA peptide vaccines. During Stage 1, poly-ICLC was not available for purposes of comprehensive clinical development and commercialization; for this reason, imiquimod, which activates immune cells through the TLR-7, was used as an immunostimulatory adjuvant, along with granulocyte macrophage-colony stimulating factor (GM-CSF). In a preclinical study, the combined use of imiquimod and GM-CSF has been demonstrated to induce a significantly greater immune reaction than either immunoadjuvant administered alone (Hilf 2010), and clinically the combination has been observed to be safe and well tolerated in the treatment of colorectal cancer using another cancer vaccine (Kuttruff 2012; Maughan 2012; Mayer 2012). In Stage 1 of this protocol, a complete dose of study drug consists of the administration of a sequence of 3 agents – SL-701 emulsion injection, GM-CSF injection and imiquimod topical cream – within an approximate 5-minute time frame. Topical application of imiquimod cream at the injection site is repeated at 24 hours (h) after each SL-701 emulsion injection. In Stage 2 of the protocol, a complete dose of study drug consists of the administration of a sequence of 2 agents – SL-701 emulsion injection and poly-ICLC injection within an approximate 20-minute time frame, with concomitant intravenous (IV) bevacizumab. (The rationale for this modification to the vaccine adjuvants is provided in Section 1.2.5.)

1.2.2 Rationale for Immunotherapy in Glioma

Although the CNS has historically been considered an immune privileged site, several clinical examples highlight the ability of the immune system to effectively attack targets within the CNS, including multiple sclerosis, encephalitis, and paraneoplastic cerebellar degeneration (Albert 1998). Experimental autoimmune encephalomyelitis (EAE) represents a further example of a potent immune response, in this case mediated by T cells, targeting specific CNS structures. EAE is extensively utilized to model the pathology of acute disseminated encephalomyelitis and multiple sclerosis in humans (Handel 2011).

Several early phase clinical studies demonstrated the safety and preliminary therapeutic benefit of peripheral vaccinations using autologous, tissue-derived glioma antigens among adult malignant glioma patients (Fadul 2011; Wheeler 2008; Yu 2004; Yu 2001; Liau 2005; Rutkowski 2004; De Vleeschouwer 2008; Yamanaka 2003; Yamanaka 2005). One of the first such approaches (Rindopepimut; Celldex Pharmaceuticals) evaluated the immune response against a 13-amino acid peptide derived from epidermal growth factor receptor variant III (EGFRvIII), a tumor-specific antigen expressed in 25-30% of GBM tumors (Wong 1992; Heimberger 2005). In a Phase 2 study conducted among newly diagnosed GBM patients with resected, EGFRvIII-expressing tumors, Sampson reported a median OS of 26.0 months. In comparison, a historical control cohort, matched for age, degree of resection, TMZ treatment and EGFRvIII expression achieved a median OS of 15.0 months following standard GBM therapy with surgery, RT, and TMZ chemotherapy (Sampson 2010). Of note, among patients who subsequently underwent resection at the time of tumor progression, EGFRvIII-expressing

tumor cells were no longer detected from 9 of 11 (82%) patients treated with Rindopepimut. These results suggest that a tumor antigen-specific immune response can effectively eliminate its targeted tumor cell population within malignant glioma tumors. Nonetheless, the detection of EGFRvIII-negative tumor cells at progression suggests that resistance can be mediated by expansion of a tumor cell subpopulation not targeted by the immune response. This mechanism of adaptability, referred to as immune escape, highlights the need for future vaccine strategies to target multiple tumor-associated antigens (TAA) in order to minimize the ability of tumors to expand antigen-negative tumor cell populations as a means of evading the immune system.

One approach to target multiple TAA is the use of whole glioma lysates to stimulate the immune system. Although the use of such an approach raises a theoretical concern for auto-immune responses against normal CNS tissues, serious auto-immune encephalitis has not been reported with this approach thus far (Yamanaka 2003; Yamanaka 2005; Yu 2004; Yu 2001; Liau 2005; Wheeler 2008; Rutkowski 2004; De Vleeschouwer 2008; Fadul 2011). Nevertheless, GAA vaccines in the form of synthetic peptides would be expected to greatly reduce the risk of treated patients developing autoimmune encephalitis. In addition, a more practical limitation to the use of whole glioma cell vaccines is the considerable and time-consuming *ex vivo* manipulation of fresh glioma explants required to generate clinical grade vaccines. In a previous study incorporating whole glioma lysates, the generation of a sufficient number of vaccine cells took 6 to 7 weeks, which may have limited the suitability of this protocol for patients presenting with large tumor burdens or those who are at a higher risk of tumor progression with a limited life expectancy (Okada 2000).

1.2.3 Rationale for the Selected GAA Targets

Numerous preclinical and proof-of-concept clinical studies with the components of the SL-701 vaccine have been conducted. Based on previous preclinical studies the GAAs targeted by the SL-701 vaccine have low or undetectable expression on most normal tissues, but are up-regulated in the majority of adult and pediatric glioma. These targets have been studied in human tumor murine models designed to assess preclinical indices of immunogenicity, as well as overall safety and autoimmune responses. In addition, several clinical studies have assessed the safety of targeting these antigens in humans, many of which have used the exact peptides present in the SL-701 vaccine. A summary of the efficacy and safety of targeting these antigens in investigator-sponsored clinical studies of GAA peptide vaccines as a treatment for glioma is provided in Section 1.3. In addition, the safety of Survivin-based vaccines as an immunotherapy approach in cancer patients has been established in several clinical studies (Otto 2005; Fuessel 2006; Wobser 2006; Tsuruma 2004).

1.2.4 Rationale for the Selected Emulsifying Agent

In the 3 investigator-sponsored GAA vaccine studies summarized in Section 1.3 that involved subcutaneous (SC) injections of emulsified vaccine, Montanide ISA-51was used as the emulsifying agent. Given the favorable safety profile of the emulsified vaccine in these studies, Montanide ISA-51 is the emulsifying agent to be used in this study. In addition, Montanide ISA-51 has been safely administered to more than 200 research patients to date and has induced T-cell responses against the immunizing peptides in a majority of patients without major toxicities (Mavroudis 2006; Bolonaki 2007; Valmori 2007; Hamid 2007; Celis 2007). Toxicities most commonly observed include local discomfort, induration, and erythema at the injection site.

1.2.5 Rationale for the Selected Vaccine Adjuvants

In 4 of the 5 investigator-sponsored GAA vaccine studies summarized in Section 1.3, the TLR agonist poly-ICLC was used as the vaccine adjuvant. While the combination of the GAA peptide vaccine and this adjuvant was generally safe and well tolerated, poly-ICLC was not available for comprehensive clinical development and commercialization during Stage 1 of this study. The adjuvants that were used in Stage 1 of this protocol consisted of imiquimod, another TLR agonist, and GM-CSF and with the intent of demonstrating efficacy with an improved safety profile relative to poly-ICLC (Disis 2002; Staehler 2007; Pilla 2006; Peoples 2008; Tjoa 1998; Adams 2008; Fenoglio 2013; Smith 2010). The justification for co-administration of imiquimod and GM-CSF was based on preclinical data indicating that the combination induces significantly greater immune reactivity than either immunoadjuvant administered alone (Hilf 2010), which has been confirmed in the clinical setting in the treatment of colorectal cancer (Kuttruff 2012).

During Stage 2 of the study, poly-ICLC is the designated vaccine adjuvant, without the administration of topical imiquimod or GM-CSF. The rationale for poly-ICLC includes its extensive prior use as an anticancer vaccine adjuvant, including its use in prior investigator-sponsored GAA vaccine studies, and the relatively high rates of early treatment discontinuation due to PD observed during Stage 1 of the current study (not observed in prior investigator-sponsored GAA vaccine studies incorporating poly-ICLC) (Okada 2011; Pollack 2014).

Poly-ICLC is a double-stranded RNA (dsRNA) and was initially evaluated as an anticancer interferon inducer in clinical studies during the 1980s (Levy 1985). These initial high-dose studies were notable for considerable toxicity and limited efficacy. In more recent decades, investigations incorporating more modest doses (10-50 μg/kg) have evaluated this agent in pediatric and adult gliomas, in both treatment-naïve and recurrent settings, both as monotherapy and in combination with other therapeutic modalities, including radiation therapy (Salazar 1996; Butowski 2009a; Butowski 2009b; Hartman 2014). Results of these clinical studies indicate a favorable safety profile, although likely limited anticancer activity as a monotherapy in adult brain cancers. Poly-ICLC is believed to activate T-lymphocytes and other immune cell populations by means of TLR3 stimulation, and has been shown to enhance the efficacy of GAA-targeting vaccine therapies in multiple controlled preclinical studies (Zhu 2007; Zhu 2010).

1.3 Studies of GAA Vaccines Using IL-13Rα2, EphA2, and/or Survivin

Table 1 summarizes the characteristics of 5 investigator-sponsored clinical studies of GAA peptide vaccines using IL-13Rα2, EphA2, and/or Survivin in adult glioma (4 studies) and pediatric glioma (1 study). Forty-eight adult patients and 33 pediatric patients with HGG or LGG in various settings have been evaluated through June 2013.

Table 1: Characteristics of Clinical Studies of Similar GAA Peptide Vaccines (June 2013)

Study Number	Study Title	Vaccine Administration and Regimen	Peptide Antigens	Emulsifying Agent	Vaccine Adjuvant	# Pts Treated
04-136	A Pilot Evaluation of Vaccination with Type-1 Dendritic Cells Pulsed with Multiple Peptides in the Adjuvant Treatment of HLA-A2 Positive Patients with Recurrent Malignant Gliomas	Four IN injections of loaded DCs every 2 wks for up to 4 vaccinations	IL-13Rα2 EphA2 YKL-40 PADRE	n/a	none	3
05-115	A Phase I/II Evaluation of Vaccination with Type-1 Dendritic Cells Pulsed with Multiple Peptides in the Treatment of HLA-A2 Positive Patients with Recurrent Malignant Gliomas	Four IN injections of loaded DCs every 2 wks for up to 4 vaccinations administered with IM injection of poly-ICLC twice per week for 8 wks	IL-13Rα2 EphA2 YKL-40 GP100 PADRE	n/a	poly-ICLC	22
07-057	A Bi-Institutional Pilot Study to Evaluate the Effects of Vaccinations with HLA-A2-Restricted Glioma Antigen-Peptides in Combination with Poly-ICLC for Adults with WHO Grade II Low-Grade Gliomas	SC injection of emulsified vaccine every 3 wks administered with IM injection of poly-ICLC on the day of and on day 4 after each vaccine for up to 8 vaccinations	IL-13Rα2 EphA2 Survivin[1] WT1 TETA830	Montanide[2]	poly-ICLC	13
08-135	A Pilot Study to Evaluate the Effects of Vaccinations with HLA-A2-Restricted Glioma Antigen-Peptides in Combination with Poly-ICLC for Adults with Recurrent WHO Grade II Gliomas	SC injection of emulsified vaccine every 3 wks administered with IM injection of poly-ICLC on the day of and on day 4 after each vaccine for up to 8 vaccinations	IL-13Rα2 EphA2 Survivin[1] WT1 TETA830	Montanide[2]	poly-ICLC	10
PRO-08030085	A Pilot Study to Evaluate the Effects of Vaccinations with HLA-A2-Restricted Glioma Antigen-Peptides in Combination with Poly-ICLC for Children with Newly Diagnosed Malignant or Intrinsic Brain Stem	SC injection of emulsified vaccine every 3 wks administered with IM injection of poly-ICLC for up to 8 vaccinations	IL-13Rα2 EphA2 Survivin[1] TETA830	Montanide[2]	poly-ICLC	33

DC = dendritic cell; GM-CSF = granulocyte macrophage colony-stimulating factor; IM = intramuscular; IN = intranodal; n/a = not applicable; poly-ICLC = Hiltonol; SC = subcutaneous; pts = patients; TBD = to be determined; wks = weeks; yrs = years

[1] Survivin peptide used is 9 amino acids; SL-701 Survivin is a 10 amino acid peptide

[2] Montanide ISA-51 (GAA/TT vaccines)

Studies 04-136 and 05-115 have been conducted under FDA IND 12415, and Studies 07-057, 08-135, and PRO08030085 have been conducted under FDA IND 13624. The following sections summarize safety and efficacy results from 2 of these studies, 05-115 and PRO08030085, since these studies enrolled patients that are most similar to the target GBM patient population (05-115) or utilized a peptide vaccine regimen that is most similar to the regimen in the present study (PRO08030085).

1.3.1 Pediatric Study – PRO08030085

The GAA peptide vaccine utilized in PRO08030085 contains the same peptides (ie, contains peptides targeting the same antigens) and was emulsified in the same agent as SL-701; the GAA Peptide Vaccine differs from SL-701 only in that the Survivin peptide utilized in PRO08030085 is a 9-mer peptide, which is not available for the purposes of comprehensive clinical development and commercialization. The Survivin peptide in SL-701 is a 10-mer peptide with similar immunoreactivity. In addition, the TLR-3 ligand poly-ICLC was used as an immunostimulatory adjuvant in PRO08030085. Since poly-ICLC is not an FDA-approved drug and is not available for purposes of comprehensive clinical development and commercialization, both imiquimod, which activates immune cells through TLR-7, and GM-CSF are being used together as immunostimulatory adjuvants with SL-701 in Stage 1. The amount of each peptide administered is 0.3 mg each of the IL-13Rα2, EphA2, and Survivin peptides and 0.2 mg of the TetA830 peptide.

As of June 2013, 33 pediatric patients have been enrolled and treated with GAA Peptide Vaccine in PRO08030085. Patient-level safety data through March 21, 2012 from 28 of these patients are available to Stemline and described below. Eligible patients were required to have a diagnosis and treatment history of one of the following:

- Newly diagnosed diffuse intrinsic pontine glioma (DIPG) or any biopsy proven HGG involving the brainstem, collectively referred to as brain stem glioma (BSG);
- Newly diagnosed, incompletely resected (ie, definite residual tumor visible on imaging) non-brainstem HGG;
- Unresectable, progressive LGG of any subtype that has recurred despite 2 prior chemotherapy or biological therapy regimens and/or radiation therapy.

Eligible HGG histologies included GBM, anaplastic astrocytoma (AA), or gliosarcoma. Other eligibility criteria included baseline Karnofsky/Lansky performance status (PS) ≥50; HLA-A2 positivity based on flow-cytometry; aged ≥3 years to <21 years; normal organ function (absolute neutrophil count [ANC] ≥1.0× 10^9/L, platelet count ≥100× 10^9/L, hemoglobin ≥8 g/dL, normal serum creatinine or glomerular filtration rate ≥70 mL/min/1.73 m^2, bilirubin ≤1.5 × upper limit of normal [ULN], alanine aminotransferase [ALT] < 3× ULN); no overt cardiac, gastrointestinal, pulmonary, or psychiatric disease; and no or low-dose corticosteroids for at least 1 week prior to enrollment.

Patients received GAA Peptide Vaccine emulsified in Montanide® ISA-51 (Seppic, Inc., Fairfield, NJ) as an SC injection every 3 weeks administered with a 30 μg/kg IM injection of poly-ICLC (Oncovir, Inc., Washington, DC). The treatment plan was to continue administration for up to 8 vaccinations, although some patients received >8 vaccinations.

Table 2 summarizes the demographics, baseline disease characteristics, and vaccine administration for the enrolled patients. All but 2 patients received RT, which was routinely initiated within a few weeks of diagnosis.

Table 2: Patient Demographics, Baseline Disease Characteristics, and Vaccine Administration: Study PRO08030085

Parameter	All Patients (N=28)
Median Age at Diagnosis, years (range)	7.2 (1.8, 17.9)
Gender, n (%)	
Male	14 (50.0)
Female	14 (50.0)
Disease, n (%)	
BSG	17 (60.7)
Newly Diagnosed HGG	5 (17.9)
Recurrent LGG	3 (10.7)
Recurrent HGG	3 (10.7)
Karnofsky/Lansky PS, n (%)	
50	1 (3.6)
60	0
70	0
80	3 (10.7)
90	10 (35.7)
100	13 (46.4)
Missing	1 (3.6)
Received Radiation, n (%)	
Yes	26 (92.9)
No	2 (7.1)
Received Chemotherapy, n (%)	
Yes	16 (57.1)
No	12 (42.9)
Median Time from Diagnosis to Start of Radiation, months (range)	0.6 (0.1, 47.1)
Median Time from Diagnosis to First Vaccine Administration, months (range)	3.9 (2.7, 189.2)
Median Number of Vaccine Doses, n (range)	5 (1, 12)

BSG = brain stem glioma; HGG = high-grade glioma; LGG = low-grade glioma.

A summary of treatment-emergent adverse events (TEAEs) (ie, event onset date was any time after the administration of the first dose of study vaccine, or the event was reported prior to first dose date and worsened after the initiation of study drug) occurring in ≥20% of all treated patients, regardless of

relationship to study drug, is presented in Table 3, by Medical Dictionary for Regulatory Activities (MedDRA), version 15.0, preferred term (PT). All but 2 TEAEs were Grade 1-2; one patient experienced Grade 3 peripheral motor neuropathy that was judged to be unrelated to study drug, and another patient experienced Grade 3 vomiting that was judged to be unlikely related to study drug. There were no serious adverse events (SAEs) or manifestations of autoimmunity (eg, vitiligo) reported. These safety summaries in Table 3 exclude cases of possible immunologically-mediated pseudoprogression.

Table 3: Summary of Treatment Emergent Adverse Events Occurring in ≥20% of All Patients: Study PRO08030085

MedDRA Preferred Term	All Patients (N=28) n (%)
Injection Site Reaction	26 (92.9)
Induration	25 (89.3)
Pyrexia	20 (71.4)
Fatigue	18 (64.3)
Vomiting	10 (35.7)
Decreased Appetite	9 (32.1)
Nausea	9 (32.1)
Headache	8 (28.6)
Constipation	7 (25.0)
Chills	6 (21.4)
Contusion	6 (21.4)

Seven (25.0%) patients had radiographic evidence of possible immunologically-mediated pseudoprogression. The median (range) number of vaccinations prior to the detection of pseudoprogression was 5 (2, 11), and 5 of the 7 patients resumed vaccinations following improvement of symptoms. All but one case was associated with clear-cut, transient neurologic deterioration. The deterioration was most significant in the patients with BSG and in 2 patients was sudden and severe in onset, and temporally related to vaccine administration.

In an update of this 33-patient study, which included 20 patients with BSG (Pollack 2013), 4 of 5 patients with BSG who experienced possible pseudoprogression survived at least 18 months after diagnosis compared to 3 of 15 patients with BSG without manifestations resembling pseudoprogression (Fisher's exact test p=0.03). This suggests that pseudoprogression does not necessarily lead to a worse outcome and in fact may be a surrogate for vaccine-mediated biological activity resulting in an improved outcome. (It should be noted that pseudoprogression has been observed in the context of both standard and investigational therapies in GBM (Van Mieghem 2013) and that pseudoprogression has been documented in other tumor types, most notably metastatic melanoma, specifically with agents

designed to augment an immune response, including those associated with prolongation of survival (Wolchok 2009; Wolchok 2010).

Based on radiographic evidence, 1 patient with HGG experienced a prolonged disease-free status on magnetic resonance imaging (MRI) during vaccination after a prior tumor resection and 3 patients experienced a partial response (PR; BSG, newly diagnosed non-brainstem HGG, and multiply recurrent LGG). Five patients recently initiated treatment and therefore were not fully evaluated for tumor response.

Median survival from date of diagnosis was 19.5 months for all patients (14 deaths among 28 patients) and 13.0 months among the subset of patients with recently diagnosed BSG (9 deaths among 16 patients). This median survival is longer than that reported in a large (n=130), Phase 3 study of RT versus RT plus chemotherapy in pediatric patients with diffuse BSG (8.0 and 8.5 months, respectively) (Broniscer 2004).

In an update of the study that includes 24 patients with newly diagnosed HGG involving the brainstem (BSG; n=20) or patients with newly diagnosed HGG involving the non-brainstem region (NBSG; n=4) (Pollack 2013), median survival was 13.2 months and 20.1 months, respectively. Two of 24 patients had PD during the first 2 courses of therapy. Among the remaining patients, the best radiographic response was stable disease (SD) in 18, PR in 2, minor response in one, and sustained disease-free status in 1 HGG patient who had undergone prior gross total resection following vaccine treatment. Among the 5 patients with pseudoprogression, one exhibited a subsequent PR and survived for 19.5 months, and the other 4 patients survived for intervals of 18.4, 19.5, 11.3, and >29.7 months, retrospectively. It is notable that the patient with pseudoprogression who subsequently stopped vaccine therapy and survived >29.7 months experienced a PR to subsequent chemotherapy (persisting 29.7 months post-diagnosis). Median OS among BSG patients with pseudoprogression was 19.5 months compared to 12.4 months in those without pseudoprogression and, as noted above, a significantly higher proportion of patients with pseudoprogression survived at least 18 months, suggesting that pseudoprogression may relate to favorable biological activity.

1.3.2 Adult Study 05-115

As of June 2013, 22 patients have been enrolled and treated with dendritic cell (DC) vaccine in Study 05-115. Safety and efficacy data presented below are from publications and presentations of the study data (Okada 2011).

Eligible patients had histological diagnosis of GBM or anaplastic glioma (AG), including AA, anaplastic oligodendroglioma (AO), anaplastic oligoastrocytoma (AOA), or other anaplastic glioma. Other eligibility criteria included up to 2 previous recurrences; baseline Karnofsky PS (KPS) ≥ 60; HLA-A2 positivity based on flow cytometry; ≥18 years of age; adequate organ function, as evidenced by granulocyte count $\geq 2.5 \times 10^9$/L, lymphocytes $\geq 0.4 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, hemoglobin ≥10 g/dL, left ventricular ejection fraction ≥50%, serum creatinine < 1.5 × ULN, bilirubin ≤2.0 × ULN, and ALT, aspartate transaminase (AST), gamma-glutamyl transferase, lactic dehydrogenase, and alkaline phosphatase <2.5 × ULN; no serious concurrent medical illness; and no or low-dose corticosteroids.

Patients received vaccinations at 1 of 2 αDC1 dose levels (1×10^7/dose or 3×10^7/dose) at 2-week intervals intranodally for up to 4 vaccinations. Participants also received twice weekly IM injections of 20 µg/kg poly-ICLC.

The median age (range) of treated patients was 48 (28, 71) years and 47% of the patients were female. Thirteen patients had GBM, 5 patients had AA, and 3 had AO, and 1 had AOA. Eleven patients received 1×10^7/dose and 11 patients received 3×10^7/dose. Nineteen patients received ≥4 vaccines.

TEAEs (possibly, probably, or definitely related to the vaccine and/or poly-ICLC administration) that occurred in ≥20% of patients included injection site reactions (82%), fatigue (73%), myalgia (32%), headache (32%), body ache (27%), and fever (23%). A patient with recurrent AO who had achieved a complete response (CR) (>29 months duration [ongoing]) experienced a Grade 4 anaphylactic reaction following the 18th dose of vaccine during the second booster phase (1×10^7 αDC1/dose). Within several minutes following intranodal αDC1 administration, this patient demonstrated systemic urticaria and hypotension, which was managed with hydration, corticosteroids, and vasopressors. Although the patient recovered with this management, the patient was admitted to the hospital overnight. This was considered a dose-limiting toxicity, and the patient was withdrawn from the study. This was the only dose-limiting toxicity observed in this study.

Among 19 patients evaluable for response based on radiographic evidence using Macdonald criteria (Macdonald 1990), 2 patients (AA, AO) experienced a CR and 3 patients (all with GBM) experienced a PR. Median OS from study entry was 12 months for the patients with GBM and >23 months for the patients with AG. This GBM survival value is consistent with the median OS of 12 months reported for patients receiving optimal therapy with surgical resection, RT, and chemotherapy.

1.4 Summary of Benefits and Risks

Despite advances in therapeutic strategies, including surgical resection, RT, chemotherapy, and targeted agents, the prognosis for many patients with brain tumors remains poor. The lack of effective treatment options for patients has been a motivation for the development of alternative therapies, including immunotherapies. This includes specific T cell epitope-based vaccines, which are under development as a potentially safer approach with greater feasibility than whole glioma cell-based vaccines.

Through June 2013, 48 adult patients and 33 pediatric patients with HGG (brainstem and non-brainstem) or LLGs in various settings have been treated with GAA peptide vaccines using Survivin, TetA830, and/or IL-13Rα2 and EphA2 in 5 investigator-sponsored studies. The results of these studies, which provided the foundation for SL-701 and justification of the planned clinical program, indicate clinical activity in the form of objective responses based on radiographic evidence, with an acceptable safety profile without raising the patient risk profile.

In the present study, the amount of each peptide administered during each dose of SL-701 emulsion is similar to that used in studies 07-057, 08-135, and PRO08030085, and the frequency of administration is similar to Study 05-115 (Table 1). In each of these studies of GAA Peptide Vaccines, the vaccinations were well tolerated, providing a rationale for the SL-701 dosing regimen in adults with glioma. The emulsifying agent Montanide ISA-51 was used in studies 07-057, 08-135, and PRO08030085, where in each case the GAA Peptide Vaccine emulsion was well tolerated. Also, the doses of the vaccine adjuvants GM-CSF and imiquimod used in Stage 1 are similar to those used in other clinical studies where minimal associated toxicity was observed (Kurtruff 2012, Disis 2002, Adams 2008, Fenoglio 2013).

While there are similarities to the GAA Peptide Vaccines used in the studies described in Section 1.3, the present study will be the first clinical study of the SL-701 regimen. Although the prior experiences of the components of the SL-701 regimen indicate acceptable safety profiles, the present study will

include an intensive safety monitoring plan, including halting of enrollment for unacceptably high rates of regimen-limiting toxicities (RLTs) or sudden or unexpected deaths related to SL-701.

Although imiquimod (Stage 1 only), GM-CSF (Stage 1 only) and poly-ICLC (Stage 2 only) are associated with known adverse events (detailed in Section 4.5), these are predominantly mild-moderate in severity and unlikely to result in unacceptable toxicity, especially given that the dosing for these agents stipulated in the current protocol entails considerably less frequent administration than in the pivotal studies from which risk-benefit profile for these agents was established. The known risk profile of these agents is additionally justified by the very limited prognosis of recurrent GBM, for which there are no available therapies proven to prolong survival.

1.5 Rationale for Use of Poly-ICLC in Stage 2

An interim analysis following enrolment of the initial 42 patients in this study (receiving SL-701, GM-CSF and topical imiquimod) indicated relatively high incidences of discontinuation during or immediately following the initial 16 weeks of study therapy. Specifically, a preliminary analysis based on data as of April 3, 2015 (and confirmed subsequently) indicated that 23 of 26 initial evaluable patients (88.5%) had discontinued therapy at or prior to the 16 week disease assessment, the majority because of PD or suspected PD. Prior and concomitant evaluations, including those performed by the Independent Data Monitoring Committee (IDMC), indicated an acceptable safety profile. Specifically, a May 2015 evaluation indicated that among the initial 41 patients receiving investigational therapy, no patient had experienced Grade 3 or higher adverse events (AEs) considered related to SL-701 or discontinued therapy because of AEs considered related to SL-701. Due to unexpected low efficacy observed during Stage 1 of this protocol, accrual was interrupted after an initial 46 patients had been enrolled, pending evaluation and development of a protocol amendment to incorporate Stage 2.

Preliminary correlative assessments also indicated evidence of T-lymphocyte recognition/activation of the vaccine epitopes. Because the time required for cell mediated immune responses may exceed the initial 8 or 16 week assessment periods, and because of the rapid growth of recurrent/relapsed GBM, it was determined that additional evaluation of the vaccine would be optimized by co-administration of the immune-adjuvant poly-ICLC, which was employed in the majority of prior investigator-sponsored clinical studies and with which GAA-vaccine administration was associated with durable GBM disease control and response. It was additionally hypothesized that increased chronologic frequency of vaccine/adjuvant therapy during the initial weeks of therapy would optimize vaccine epitope-mediated anti-GBM immune response, as has been demonstrated in several pre-clinical investigations (Wick 2011; Cho 2013).

1.6 Rationale for Addition of Bevacizumab in Stage 2

It has been hypothesized that the potential efficacy of SL-701 could be optimized by concomitant administration of an agent known to confer disease stabilization over several weeks or months, such as bevacizumab. Additionally, pre-clinical evaluations indicate that inhibition of VEGF-mediated tumor neoangiogenesis may enhance immune recognition of neoplasia and concomitant anticancer immune mechanisms (Huang 2012; Schoenfeld 2011; Tartour 2011).

The safety profile associated with SL-701 in combination with poly-ICLC in prior investigator-sponsored research, the safety profile associated with SL-701 in the early portion of STML-701-0114, and the known (non-overlapping) safety profile of bevacizumab suggest that a combination of these agents would also have a high likelihood of an acceptable safety profile.

2. STUDY OBJECTIVES

The objectives of this study are to characterize the efficacy and safety of SL-701 as a treatment for recurrent GBM.

2.1 Primary Objectives

The primary objectives are to:

- Characterize the safety and tolerability of SL-701 and SL-701 in combination with bevacizumab.
- Estimate the percent of patients alive 12 months after the initiation of SL-701 (OS-12).
- Estimate the ORR.

2.2 Secondary Objectives

The secondary objectives are to:

- Estimate the duration of response (DR).
- Estimate the percent of patients alive and PFS-6 after the initiation of SL-701.
- Estimate the distributions of PFS and OS.

2.3 Exploratory Objectives

The exploratory objectives are to:

- Estimate the relationships between measures of immunogenicity and anti-tumor efficacy.
- Evaluate available post-vaccine tumor tissue for GAA expression status and infiltration of GAA-specific T-cells.

3. INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a multicenter, open label Phase 1/2 study evaluating the efficacy and safety of SL-701 as a treatment for recurrent GBM, divided into 2 stages. Approximately 76 patients will be treated in the study, 46 in Stage 1 and 30 in Stage 2, men and women at least 18 years of age, all of whom must have shown unequivocal evidence of either a first tumor recurrence or progression during or following an initial treatment regimen before enrollment in this study. At least 56 of the 76 treated patients must have measureable disease based on contrast enhanced MRI or computed tomography (CT) scans.

During Stage 1, patients will receive SL-701 with the vaccine adjuvants GM-CSF injection and imiquimod topical cream. The first 24 patients treated in Stage 1 will be subject to the toxicity monitoring rules described under Safety Assessments (Section 3.2.1). Progression of disease and disease-related death will not be considered AEs. During Stage 2, patients will receive SL-701 with the vaccine adjuvant poly-ICLC and bevacizumab. The expected enrollment time frame for this clinical study is 12 months after accrual is open for the study.

Patients who consent to the study will have screening procedures completed (Days -13 to 0, with the exception of HLA testing which may be conducted 28 days prior to the start of investigational therapy).

In Stage 1, a complete dose of study drug consists of the administration of a sequence of 3 agents, SL-701 emulsion SC injection, GM-CSF SC injection, and imiquimod topical cream, within a 5-minute time frame. Topical application of imiquimod cream at the injection site is repeated at 24 h after each SL-701 emulsion injection. For each patient, SL-701 emulsion (SL-701 in Montanide®) will be administered by SC injection beginning on Day 1 with imiquimod topical cream 5% applied immediately (within 5 minutes after SL-701 emulsion injection) to the SL-701 emulsion injection site. In addition to the SL-701 emulsion injection, the patient will receive a SC injection of GM-CSF 150 µg close to the injection site of SL-701 emulsion (immediately following the SL-701 emulsion injection, prior to the application of topical imiquimod). An additional dose of imiquimod cream will be applied at the same site by the patient 24 h later.

In Stage 2, a complete dose of investigational treatment consists of the administration of a sequence of 2 agents, SL-701 emulsion SC injection and poly-ICLC IM injection, within an approximate 20 minute time frame. In Stage 2, patients also will receive IV bevacizumab (10 mg/kg) administered every 2 weeks, subsequent to the administration of SL-701/poly-ICLC. Investigational SL-701 emulsion (and the adjuvant poly-ICLC) will be administered twice weekly for the initial 2 weeks, every 7 days during the subsequent 3 doses, and subsequently every 14 days for the subsequent 9 doses (16 doses total) through Study Week 22, followed by every 4 weeks (for SL-701/poly-ICLC) until study end (bevacizumab will continue to be administered every 2 weeks subsequent to Week 22). Patients will continue to receive study drugs according to this schedule until the occurrence of PD, withdrawal of informed consent, unacceptable toxicity, or non-compliance, whichever occurs first.

On days of study drug administration, patients will have concomitant medications recorded, vital signs and weight measured, blood samples taken for serology and laboratory chemistry evaluation, and urine taken for urinalysis. Clinical status will be assessed for significant changes at each visit to the study site and AEs will be documented. During Stage 1, patients will also receive a paper diary to remind them how to apply imiquimod 24 h after the SL-701 emulsion injection and to document their imiquimod use. After Day 1, study staff will collect these diaries and the unused portion of imiquimod packet at each study visit and at the End of Treatment visit. During Stage 1, the Study Week 2 visit includes the second SL-701 emulsion and adjuvant administration and must be done at exactly 2 weeks after the Day 1 SL-701 emulsion administration date. Study visits and assessments after the second SL-701 emulsion administration (Week 2) should be done within a ± 3 day window adhering to the schedule in Table 4 (Stage 1) and Table 5 (Stage 2).

Blood samples (60 mL per day) for immunological monitoring studies will be collected on Study Day 1, at Study Weeks 4, 8, 12, 16,and 24, and then every 8 weeks thereafter (approximately) to evaluate the magnitude of immune response in peripheral blood mononuclear cells (PBMC) against the targeted GAA peptides using IFN-γ- ELISPOT assay, major histocompatibility complex (MHC) tetramer assay, and flow cytometric analyses of lymphocyte activation. Tumor tissue samples, whenever there is available pretreatment tissue or tumor is biopsied for any reason throughout the duration of the study, will be archived and assessed for GAA expression status and infiltration of GAA-specific T-cells.

Approximately every 8 weeks after Day 1, each patient will undergo a MRI or CT scan (the same modality as used to qualify for study entry). Scans should be performed every 8 weeks (± 7 days; ± 5 days for the scan performed at Study Week 8). The interpretations of these imaging scans will be used to assess objective tumor response. Each tumor response assessment will use modified Response Assessment in Neuro-Oncology (RANO) criteria and information will be collected on the patient's

clinical status (eg, stable, improved, or declining since the last assessment), functional neurological status (KPS score) and concomitant medications, including corticosteroid use.

Within 2 weeks of the determination of a patient's permanent discontinuation of study drug, the patient will return to the clinic for an "End of Treatment Visit". At this visit the patient will receive a physical examination (including assessment of vital signs and weight), KPS score, and AEs and concomitant medications will be recorded. In accordance with current Good Clinical Practice and regulations, AEs will be recorded and monitored for 30 days after the last dose of study drug. Disease progression in the medical opinion of the physician and/or disease-related morbidity and mortality as a study endpoint will not be considered an AE or SAE. In addition, survival status and documentation of subsequent salvage therapy will continue to be collected by telephone call approximately every 90 days after the last dose of study drug.

Table 4 provides the schedule of events for the study during Stage 1.

Table 5 provides the schedule of events for the study during Stage 2.

Table 4: Study Event Schedule: Stage 1

Study Visits	Screening: Day -13 to 0	Day 1	Weeks 2, 4, and 6	Week 8	Weeks 10, 12, and 14	Week 16	Weeks 18, 20, and 22	Week 24	Week 26	Week 30	Week 34	Beyond Week 34		End of Treatment	Safety: Through 30 Days After Last Dose	Survival Every 90 Days After Last Dose
												Every 4 wks	Every 8 wks			
Study Procedures																
Informed consent form	X															
Inclusion/exclusion criteria[0]	X															
Medical history including prior therapy[1]	X															
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
Physical examination	X		X week 4	X	X week12	X	X week 20		X	X	X	X		X		
Pregnancy test [2]	X													X		
Vital signs[3] and weight	X	X	X	X	X	X	X	X	X	X	X	X		X		
Hematology[4]	X	X	X	X	X	X	X		X	X	X	X		X		
Serum chemistry[5]	X	X	X	X	X	X	X		X	X	X	X		X		
Coagulation parameters[6]	X	X	X	X	X	X	X		X	X	X	X		X		
Urinalysis[7]	X	X	X	X	X	X	X		X	X	X	X		X		
SL-701, GM-CSF and imiquimod dosing[12]		X	X	X	X	X	X		X	X	X	X				
Dispense imiquimod and patient diary[12]		X	X	X	X	X	X		X	X	X	X				
Collect patient diary			X	X	X	X	X	X		X	X	X		X		

Study Visits	Screening: Day -13 to 0	Day 1	Weeks 2, 4, and 6	Week 8	Weeks 10, 12, and 14	Week 16	Weeks 18, 20, and 22	Week 24	Week 26	Week 30	Week 34	Beyond Week 34		End of Treatment	Safety: Through 30 Days After Last Dose	Survival Every 90 Days After Last Dose
												Every 4 wks	Every 8 wks			
Study Procedures																
and unused imiquimod[12]																
Phlebotomy for Immune response studies[8]		X	X week 4 only	X	X week 12 only	X		X			X		X[8]	X[8]		
MRI or CT[9]	X			X		X		X			X		X[11]			
Karnofsky Performance Status	X			X		X		X	X		X		X[11]	X		
Clinical assessment for PD[10]				X		X		X			X		X[11]	X		
Objective Tumor (response) assessment	X			X		X		X			X		X[11]			
Tumor tissue submission, as available	X	→														
AE monitoring		X	X	X	X	X	X	X	X	X	X	X		X	X	
Survival & subsequent therapy documentation															X	X

Abbreviations: MRI - magnetic resonance imaging; CT - computed tomography; AE – adverse event.
NOTE: Study Week 2 visit includes the second SL-701 emulsion and adjuvant administration and must be done 2 weeks (± 3 days) after the Day 1 SL-701 emulsion and adjuvant administration date. Study visits and assessments after the second SL-701 emulsion and adjuvant administration (Week 2) should be done within a ± 3 day window. Study Week 8 MRI or CT must be done 8 weeks (± 5 days) after the Day 1 SL-701 emulsion and adjuvant administration. MRI or CT scans after Study Week 8 should be done every 8 weeks ± 7 days. For patients with evidence of disease control ongoing beyond 50 weeks, MRI or CT scans after Study Week 50 may be performed every 12 weeks (± 14 days).
[0] Laboratory evaluation of HLA status may be performed within a 28 day period prior to initiation of investigational therapy. Unless otherwise stated, other inclusion/exclusion evaluations should be performed within a 14-day period (Days -13 through 0) prior to initial study therapy.
[1] Medical history includes surgical history, demographics, and detailed therapy for the past 28 days.

[2] Pregnancy testing may be done using a urine or serum sample.
[3] Vital signs include blood pressure, heart rate, respiratory rate, and body temperature.
[4] Hematology assessments include hematocrit, hemoglobin, red blood cell count, white blood cell count with differential (neutrophils, eosinophils, basophils, lymphocytes, and monocytes), platelet count, and reticulocytes.
[5] Serum chemistry tests include alanine aminotransferase, albumin, alkaline phosphatase, aspartate aminotransferase, blood urea nitrogen, calcium, carbon dioxide, chloride, creatine kinase, creatinine, direct bilirubin, glucose, lactate dehydrogenase, phosphorus, potassium, sodium, total bilirubin, total protein, and uric acid.
[6] Coagulation parameters assessed are prothrombin time or international normalized ratio (INR) and activated partial thromboplastin time (aPTT).
[7] Urinalysis assessments include bilirubin, blood, color, glucose, ketones, leukocyte esterase, nitrites, pH, protein, specific gravity, turbidity, urobilinogen, and microscopic examination (including bacteria, casts, crystals, epithelial cells, red blood cells, and white blood cells).
[8] Peripheral blood for immune response evaluation should be performed at baseline (Day 1), and prior to treatment at Weeks 4, 8, 12, 16, 24, 34 and thereafter every 8 weeks through Week 50. For patients remaining on-study beyond Week 50, peripheral blood should be evaluated every 12 weeks (± 14 days) and at end-of-treatment.
[9] After the first dose of study treatment, the same type of scan, MRI or CT, should be taken to assess tumor response as was used to qualify the patient for entry into the study (screening scan). MRI is the preferred imaging modality as detailed in the protocol.
[10] As part of each tumor response assessment using modified RANO criteria, information will be collected on the patient's clinical status (eg, stable, improved, or declining since the last assessment), functional neurological status (KPS score) and concomitant medications, including corticosteroid use.
[11] For patients remaining on-study beyond week 50, MRI or CT, KPS score, and tumor assessments may be performed every 12 weeks (± 14 days).
[12] Imiquimod (topical) and GM-CSF (subcutaneous) are administered during Stage 1 of the study only.

Table 5: Study Event Schedule: Stage 2

Study Visits	Screening: Day -13 to 0	Day 1	Days 4, 8, 11; Weeks 2, 3, 4, & 6	Week 8	Weeks 10, 12, and 14	Week 16	Weeks 18, 20, and 22	Week 24	Week 26	Week 30	Week 34	Beyond Week 34		End of Treatment	Safety: Through 30 Days After Last Dose	Survival Every 90 Days After Last Dose
												Every 4 wks	Every 8 wks			
Study Procedures																
Informed consent form	X															
Inclusion/exclusion criteria[1]	X															
Medical history incl. prior therapy[2]	X															
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
Physical examination	X		X wk 2 & 4	X	X week12	X	X week 20		X	X	X	X		X		
Pregnancy test [3]	X													X		
Vital signs[4] and weight	X	X	X	X	X	X	X	X	X	X	X	X		X		
Hematology[5]	X	X	X	X	X	X	X		X	X	X	X		X		
Serum chemistry[6]	X	X	X	X	X	X	X		X	X	X	X		X		
Coagulation parameters[7]	X	X	X w 2, 4, 6	X	X	X	X		X	X	X	X		X		
Urinalysis[8]	X	X	X w 2, 4, 6	X	X	X	X		X	X	X	X		X		
SL-701 and poly-ICLC dosing[9]		X	X	X	X	X	X		X	X	X	X				
Bevacizumab dosing[10]		X	X weeks 2, 4, 6	X	X	X	X	X	X	X	X	X				

Study Visits	Screening: Day -13 to 0	Day 1	Days 4, 8, 11; Weeks 2, 3, 4, & 6	Week 8	Weeks 10, 12, and 14	Week 16	Weeks 18, 20, and 22	Week 24	Week 26	Week 30	Week 34	Beyond Week 34		End of Treatment	Safety: Through 30 Days After Last Dose	Survival Every 90 Days After Last Dose
												Every 4 wks	Every 8 wks			
Study Procedures																
Phlebotomy for Immune response studies[11]		X	X week 4	X	X week 12	X		X			X		X	X		
MRI or CT[12]	X			X		X		X			X		X[13]			
Karnofsky Performance Status	X			X		X		X	X		X		X[13]	X		
Clinical assessment for PD[14]				X		X		X			X		X[13]	X		
Objective Tumor (response) assessment	X			X		X		X			X		X[13]			
Tumor tissue submission, as available	X	→														
AE monitoring		X	X	X	X	X	X	X	X	X	X	X		X	X	
Survival & subsequent therapy documentation															X	X

Abbreviations: MRI - magnetic resonance imaging; CT - computed tomography; AE – adverse event

NOTE: During the initial 2 weeks of study therapy (in Stage 2), SL-701 emulsion and adjvuant will administered twice per week. The Day 4 and Day 11 visits may be performed ± 1 day (ie, on either Days 3, 4 or 5 and on either Days 9, 10, or 11). The Day 8 (Week 1) visit should be done as closely as possible to a date 1 week after the Day 1 SL-701 emulsion administration (± 3 days is permitted). Study visits and assessments subsequent to these initial twice-weekly administrations (Week 3 and beyond) should be done within a ± 3 day window. Study Week 8 MRI or CT must be done 8 weeks (± 5 days) after the Day 1 SL-701 emulsion and adjuvant administration. MRI or CT scans after Study Week 8 should be done every 8 weeks ± 7 days. For patients with evidence of disease control ongoing beyond 50 weeks, MRI or CT scans after Study Week 50 may be performed every 12 weeks (± 14 days).

[1] Laboratory evaluation of HLA status may be performed within a 28 day period prior to initiation of investigational therapy. Unless otherwise stated, other inclusion/exclusion evaluations should be performed within a 14-day period (Days -13 through 0) prior to initial study therapy.

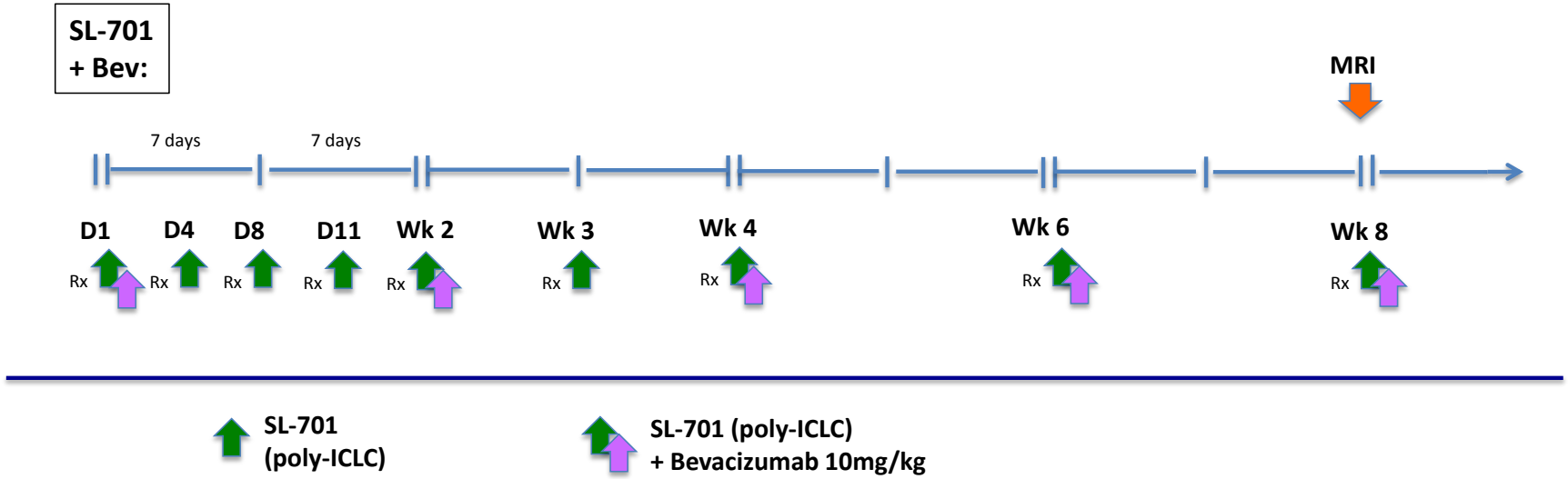
[2] Medical history includes surgical history, demographics, and detailed therapy for the past 28 days.

[3] Pregnancy testing may be done using a urine or serum sample.

[4] Vital signs include blood pressure, heart rate, respiratory rate, and body temperature.

[5] Hematology assessments include hematocrit, hemoglobin, red blood cell count, white blood cell count with differential (neutrophils, eosinophils, basophils, lymphocytes, and monocytes), platelet count, and reticulocytes.
[6] Serum chemistry tests include alanine aminotransferase, albumin, alkaline phosphatase, aspartate aminotransferase, blood urea nitrogen, calcium, carbon dioxide, chloride, creatine kinase, creatinine, direct bilirubin, glucose, lactate dehydrogenase, phosphorus, potassium, sodium, total bilirubin, total protein, and uric acid.
[7] Coagulation parameters assessed are prothrombin time or international normalized ratio (INR) and activated partial thromboplastin time (aPTT).
[8] Urinalysis assessments include bilirubin, blood, color, glucose, ketones, leukocyte esterase, nitrites, pH, protein, specific gravity, turbidity, urobilinogen, and microscopic examination (including bacteria, casts, crystals, epithelial cells, red blood cells, and white blood cells).
[9] Poly-ICLC (IM injection) is administered during Stage 2 of the study only.
[10] During study Stage 2, patients will receive SL-701 (including adjuvant) with bevacizumab. Bevacizumab will be administered at a dose of 10 mg/kg body weight and will be administered starting Day 1 and approximately every 2 weeks thereafter. On days when both SL-701 and bevacizumab are to be administered, bevacizumab should be administered following administration of SL-701 and adjuvant. For patients remaining on-study beyond Weeks 24-26, bevacizumab administration every 2 weeks should continue, including Weeks 28 and 32. Although other study procedures will occur every 4 or 8 weeks beyond Week 34 (and in some cases every 12 weeks beyond Week 50), bevacizumab administration should continue every 2 weeks until there is evidence of PD or unacceptable toxicity.
[11] Peripheral blood for immune response evaluation should be performed at baseline (Day 1), and prior to treatment at Weeks 4, 8, 12, 16, 24, 34 and thereafter every 8 weeks through Week 50. For patients remaining on-study beyond Week 50, peripheral blood should be evaluated every 12 weeks (± 14 days) and at end-of-treatment.
[12] After the first dose of study treatment, the same type of scan, MRI or CT, should be taken to assess tumor response as was used to qualify the patient for entry into the study (screening scan). MRI is the preferred imaging modality as detailed in the protocol.
[13] For patients remaining on-study beyond Week 50, MRI or CT, KPS score, and tumor assessments may be performed every 12 weeks (± 14 days).
[14] As part of each tumor response assessment using modified RANO criteria, information will be collected on the patient's clinical status (eg, stable, improved, or declining since the last assessment), functional neurological status (KPS score) and concomitant medications, including corticosteroid use.

Figure 1: Treatment Flow Schedule for Stage 2



3.2 Safety Assessments

An IDMC will be established prior to the inclusion of the first patient in the study. The IDMC will evaluate all available safety data when 10 patients have received at least 2 doses of SL-701, died, or are withdrawn from the study. During Stage 2, the IDMC will also evaluate available safety data when 10 patients have received at least 3 doses of SL-701 (and adjuvant) and bevacizumab, died, or are withdrawn from the study. The IDMC will also monitor for RLTs throughout the study (ie, beyond the first 24 treated patients) to confirm the risk of RLTs is <33%, and the Committee may recommend interruption of accrual at any time during the study if excessive toxicity is observed. Details regarding the content and timing of these safety reviews will be provided in the IDMC Charter.

3.2.1 Toxicity Monitoring Rules

The toxicity monitoring rules for the following events will be applied to the first 24 patients treated in the study. Given the possibly long latency period for the toxicities of interest, there will not be any interruption in accrual to assess these events.

3.2.2 Regimen Limiting Toxicity

RLT includes any of the following events that occur anytime through the first 12 doses of study treatment (ie, from first treatment through approximately 24 weeks), which are considered possibly, probably or definitely related to investigational therapy:

- ≥Grade3 bronchospasm or Grade 2 bronchospasm that does not resolve within 24 hours despite appropriate medical therapy (ie, inhaled albuterol);
- ≥Grade 3 generalized urticaria;
- Other ≥Grade 3 allergic reaction, such as exfoliative erythroderma, anaphylaxis, or vascular collapse;
- ≥Grade 3 non-hematologic toxicity (excluding hepatic laboratory toxicity and excluding Grade 3 hypertension in which blood pressure resolves to <160 [systolic] and <100 [diastolic] with intensified antihypertensive therapy) related to the study treatment regimen including ≥Grade 3 injection site reaction due to SL-701 or immunoadjuvant administration, with the exception of transient ≥Grade 3 events as detailed below;
- Intolerable ≥Grade 3 skin (injection site) reaction lasting ≥7 days (at Grade 3) or that recurs despite discontinuation of imiquimod, if applicable;
- ≥Grade 3 constitutional symptoms (including fatigue, fever, malaise, myalgia, edema [non-cerebral]) that persist for > 48 h and that recur and persist for > 48 h despite discontinuation of imiquimod, if applicable;
- ≥Grade 3 nausea/vomiting or diarrhea exceeding 24 h despite sufficient anti-emetic or anti-diarrheal therapy, respectively;
- Grade 3 or 4 neutropenia with fever;
- Grade 4 hematologic toxicity (cytopenia) lasting >5 days;

- Cerebral edema associated with severe clinical manifestations (Grade 4), which in the Investigator's opinion is related to study therapy. Cerebral edema (Grade 4) due to underlying tumor progression (based on imaging), change in concurrent medications (such as rapid decrease in corticosteroids), or a comorbid event (such as status epilepticus, severe electrolyte imbalance) as well as Grade <4 cerebral edema, will not be classified as RLT. Examples of this RLT include severe manifestations attributed to pseudoprogression that do not improve with medical or surgical intervention.

A review will take place following each RLT. Additionally, if a RLT occurs in ≥2 of the first 3 patients, ≥3 of the first 6 patients, ≥4 of the first 9 patients, ≥4 of the first 12 patients, ≥5 of the first 15 patients, ≥6 of the first 18 patients, or ≥7 of the first 24 patients, accrual will be suspended and the Investigator, Medical Monitor and Sponsor will make decisions regarding continuation of study accrual.

Events meeting the above criteria which occur subsequent to the first 12 doses of study treatment (ie, more than approximately 24 weeks following the start of investigational therapy) will be considered RLT-level events. Evaluation of safety data for RLT-level events will occur according to similar guidelines/parameters as defined above (for RLTs).

Please consult the appropriate components of Section 5.5 for additional criteria for the discontinuation of investigational study therapy.

3.2.2.1 Sudden or Unexpected Deaths Related to SL-701

A safety review will take place following each sudden or unexpected death that is not considered by the Investigator to be a disease-related mortality and is considered to be related to SL-701. Additionally, if such an event occurs in ≥2 of the first 3 patients, ≥3 of the first 6 patients, ≥4 of the first 9 patients, ≥4 of the first 12 patients, ≥5 of the first 15 patients, ≥6 of the first 18 patients, or ≥7 of the first 24 patients, accrual will be suspended and the Investigator, Medical Monitor, and Sponsor will make decisions regarding the continuation of study accrual. (Note: these are general guidelines, and lower rates of treatment-related deaths would likely result in study discontinuation.) Glioblastoma multiforme-related mortality and morbidity will not be reported as expedited IND safety reports, unless there is a serious and unexpected event with evidence of a causal relationship between study drug and the event.

3.2.2.2 Diagnosis and Management of Suspected SL-701-Induced Pseudoprogression

If pseudoprogression is suspected within 12 months following the initiation of SL-701 and the patient is neurologically worse sufficient to warrant the initiation of or an increase in the dosage of corticosteroids, subsequent doses of SL-701along with the applicable adjuvants (GM-CSF and imiquimod in Stage 1 and poly-ICLC with bevacizumab in Stage 2) will not be administered pending evaluation as per the guidelines described below. Pseudoprogression refers to increased enhancement of the primary tumor and/or surrounding tissue without unequivocal evidence of tumor progression on imaging that may be due to inflammation associated with study therapy, changes in relevant medications (ie, decreased corticosteroid dosing), or the development of a co-morbid event. The following is a summary of how suspected pseudoprogression will be managed within the protocol.

- If a scan shows a ≤50% increase in tumor size and the patient is asymptomatic or symptoms are sufficiently mild as to not warrant initiation of or an increase in the dosage of corticosteroids, SL-701 will be continued and clinical and imaging monitoring will continue per protocol. SL-701 should not be discontinued in the setting of unidimensional increases in contrast-enhancing tumor ≤1cm, unless there is additional clinical/radiographic evidence of unequivocal GBM progression.
- If a scan shows increased size of the enhancing tumor and the patient demonstrates worsening neurological status sufficient to warrant the initiation of or an increase in the dosage of corticosteroids, SL-701 will be held and dexamethasone will be administered or increased as clinically warranted for symptom control. Re-imaging should be performed every 4 weeks (± 7 days) (maximum 4-month duration) to determine disease status on the lowest possible corticosteroid dose. Inability to wean the corticosteroid dose to dexamethasone ≤4 mg/day during this interval will result in permanent discontinuation of SL-701.
    - If the repeat scan on increased corticosteroid dose is unchanged or worse, and/or the patient's clinical status has not improved, a biopsy (or resection, if clinically indicated) may be considered to differentiate between pseudo- and true tumor progression. When a biopsy or resection is performed, the histopathological specimen should be carefully examined for evidence of inflammatory/lymphocytic infiltration (pseudoprogression). If inflammatory/ lymphocytic infiltration and/or necrosis comprise the majority of the specimen, patients may remain on study and restart SL-701 once they are clinically stable in the opinion of the Investigator and receiving ≤4 mg/day dexamethasone for at least 7 days. If the majority of the resected specimen consists of persistent/recurrent tumor, the patient will be considered to have true tumor progression and SL-701 will be permanently discontinued.
    - In patients who refuse to undergo a biopsy or when a biopsy is prohibitive, re-imaging should be performed every 4 weeks (± 7 days) (for a maximum 4-month duration) to determine disease status and corticosteroids should be weaned if possible to ≤4 mg/day dexamethasone. If the repeat scan done after SL-701 has been held and corticosteroids have been initiated or increased is worse, and/or the patient's clinical status has declined despite the increased corticosteroid dose, the patient will be permanently discontinued from SL-701 due to presumed tumor progression. The patient may restart SL-701 provided the following criteria are met: 1) the repeat scan shows the tumor is stable or improved; 2) the patient is clinically stable or improved (even if they have partial resolution of symptoms and have not returned to pre-pseudoprogression status); and 3) there is no evidence of new tumor spread.

Patients who meet the criteria to resume treatment will be categorized as having had pseudoprogression and will be evaluated by the Investigator and treatment response will be documented as SD, PR, or CR, depending on their subsequent imaging response at re-initiation of SL-701, or if the response continues to improve.

The diagnosis of pseudoprogression can only be made in retrospect. Thus, in the setting of initial neurological worsening in the midst of SL-701 treatment, the underlying explanation may be true PD or pseudoprogression, the latter being associated with transient worsening of the clinical and imaging status that subsequently improves on corticosteroids and the improvement persists upon weaning of the corticosteroid dose. In contrast, true PD is associated with worsening that fails to improve with corticosteroid therapy or continues to progress or recurs on weaning the corticosteroids prior to additional vaccine treatment.

3.2.3 Routine Safety Assessments

Routine safety assessments include the collection of data on AEs, SAEs, physical examinations, vital sign and weight measurements, clinical laboratory evaluations, and reasons for treatment discontinuation.

The AE reporting period for each patient enrolled in the study begins from the time the patient signs the informed consent form (ICF) and is continuous through 30 days after the last dose of study treatment. All AEs that occur in enrolled patients during the adverse reporting period specified in the protocol must be collected in the study database whether or not the event is considered related to study drug treatment. Any known untoward event that occurs beyond the AE reporting period that the Investigator assesses as related to study drug treatment should also be reported as an AE.

3.2.3.1 Clinical Laboratory Testing

Blood and urine samples will be collected for clinical laboratory tests (hematology, serum chemistry, and urinalysis) according to the Study Event Schedule in Table 4 (Stage 1) and Table 5 (Stage 2).

The following clinical laboratory parameters will be measured:

Hematology	Hematocrit, hemoglobin, red blood cell count, white blood cell count with differential (neutrophils, eosinophils, basophils, lymphocytes, and monocytes), platelet count, and reticulocytes
Serum Chemistry	ALT, albumin, alkaline phosphatase, AST, blood urea nitrogen, calcium, carbon dioxide, chloride, creatine kinase, creatinine, direct bilirubin, glucose, lactate dehydrogenase, phosphorus, potassium, sodium, total bilirubin, total protein, and uric acid
Coagulation Parameters	Prothrombin time or international normalized ratio (INR), and activated partial thromboplastin time (aPTT)
Urinalysis	Bilirubin, blood, color, glucose, ketones, leukocyte esterase, nitrites, pH, protein, specific gravity, turbidity, urobilinogen, and microscopic examination (including bacteria, casts, crystals, epithelial cells, red blood cells, and white blood cells)

Local laboratories will be used for all clinical laboratory testing. Blood for laboratory evaluation may be obtained either the day of investigational therapy, or within a 72-hour period prior to treatment (with the

exception of Day 1). Please consult Section 5.3 regarding postponement/administration of investigational therapy in the setting of laboratory abnormalities.

Laboratory reports will be reviewed, signed, and dated by the Investigator or delegated physician. Clinical laboratory results outside of the reference ranges will be flagged in the data listings and evaluated for clinical significance by the Investigator.

3.2.3.2 Vital Sign Measurements and Weight

Vital sign measurements (systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, and body temperature) and weight measurement will be performed periodically throughout the study, according to the Study Event Schedule (Table 4 [Stage 1] and Table 5 [Stage 2]). Blood pressure and pulse rate will be measured after the patient has been resting in the supine position for at least 5 minutes.

3.2.3.3 Physical Examination

A complete physical examination will be performed during the Screening period, periodically during the study, and at the End of Treatment Visit (Table 4 [Stage 1] and Table 5 [Stage 2]). Height in cm will be measured once during the Screening period. The examination will include the following body systems: general appearance; eyes, ears, nose and throat, head and neck; chest and lungs; cardiovascular; abdomen; musculoskeletal; lymphatic; dermatologic; neurologic; psychiatric; and extremities. Physical examinations will be conducted by a physician or health professional listed on the Form FDA 1572 and licensed to perform physical examinations.

3.2.3.4 Site Reaction Assessment

At each study visit after Day 1, study personnel will assess the injection/application site of study drug from previous visits for evidence of cutaneous AEs.

3.2.3.5 Demographics and Medical and Medication History

Demographic information, medical history, and prior and concurrent medications, including treatments received related to any brain tumor, will be reviewed and recorded before the first dose of study drug, during the Screening period, as detailed in the Study Event Schedule (Table 4 [Stage 1] and Table 5 [Stage 2]).

3.2.4 Total Blood Sample Volume

The volume of blood collected from each patient is expected to be approximately 50 mL for clinical laboratory testing, and 60 mL for immune response testing at each collection time point (immune response samples are to be collected in 6 × 10 cc green top tubes at each time point). The total blood volume to be collected at a study visit when both clinical laboratory and immune response testing is done will be 110 mL. These schedules for these tests are shown in Table 4 (Stage 1) and Table 5 (Stage 2), Study Event Schedule.

3.3 Efficacy Assessments

Efficacy assessments include ORR, DR, OS, OS-12, PFS, and PFS-6.

In study Stage 1, clinical assessments will nominally be made every 2 weeks, starting on Study Day 1 through Study Week 22, and then every 4 weeks (28 days) after Study Week 22. In study Stage 2, clinical assessments will nominally be made twice weekly during Weeks 1 and 2, every week between Week 2 and Week 4, and then every 2 weeks through Study Week 22, and then every 4 weeks (28 days)

after Study Week 22. These study days correspond to days that SL-701 emulsion is administered to the patient at the study site. Tumor response assessments using modified RANO criteria (for ORR, DR, and progression) will be based on MRI/CT scans obtained 8 weeks after Study Day 1 (± 5 days) and then every 8 weeks (± 7 days) compared with the patient's MRI or CT scan obtained during screening for this study. Each tumor response assessment will use modified RANO criteria and information will be collected on the patient's clinical and functional neurological status and concomitant medications, including corticosteroid use. For comparative purposes, response will also be assessed by Response Evaluation Criteria in Solid Tumors (RECIST) criteria (see Appendix 14.3).

A patient with radiographic evidence of PD after initiating study drug may continue study drug for an additional 8 weeks, provided that the patient does not experience significant clinical deterioration and/or significant toxicity, as determined by the treating Investigator and Sponsor. If follow-up imaging after 8 weeks of additional study drug confirms PD relative to the scan that initially demonstrated PD, as defined above, study drug will be discontinued due to PD. SL-701 should not be discontinued in the setting of unidimensional increases in contrast-enhancing tumor ≤1cm, unless there is additional clinical/ radiographic evidence of unequivocal GBM progression. Follow-up imaging may be performed <8 weeks after the initial detection of PD (eg, after 4 weeks) if medically appropriate. If PD is confirmed on follow-up imaging at 2 consecutive time points ≥4 weeks apart, the PD date will be the date that PD criteria were initially met. Please consult Section 3.2.2.2 for additional definitions of pseudoprogression and protocol conduct in the setting of potential pseudoprogression and/or progression.

Blood samples (60 mL per day) for immunological monitoring studies will be collected on Day 1, at Study Weeks 4, 8, 12, 16 and 24, and then every 8 weeks thereafter to evaluate the magnitude of immune response in PBMC against the targeted GAA peptides using IFN-γ-enzyme-linked immuno-spot (ELISPOT) assay, MHC tetramer assay, and flow cytometric analyses of lymphocyte activation. All patient samples will be collected at the respective treatment sites and promptly shipped to a single central processing laboratory to minimize variability. Tumor tissue samples, whenever there is available pretreatment tissue or tumor is biopsied for any reason throughout the duration of the study, will be archived and assessed for GAA expression status and infiltration of GAA-specific T-cells.

Tumor response for ORR, DR, and PFS measurements will be assessed using modified RANO criteria (Appendix 14.2), based on MRI or CT scans obtained 8 weeks after Day 1 (± 5 days) and then every 8 weeks (± 7 days). As part of each tumor response assessment using modified RANO criteria, information will be collected on the patient's clinical status (eg, stable, improved, or declining since the last assessment), functional neurological status (KPS score) and concomitant medications, including corticosteroid use.

Using the modified RANO criteria (Appendix 14.2), ORR is defined as the proportion of patients achieving a best response of CR or PR on 2 consecutive MRIs obtained ≥4 weeks apart.

DR is defined as the time from the date measurement criteria are first met for objective response until the first date that the criteria for PD is met, or death due to any cause, whichever occurs first.

OS is defined as the time from the date of initiation of SL-701 to the date of death from any cause.

PFS is defined as the time from the date of initiation of SL-701 to the date of PD or death from any cause, whichever occurs first.

Efficacy assessments for a given patient should be made by the same investigator as much as possible to limit variability. In particular, efforts should be made for the same investigator to perform the measurements for a given patient throughout the study.

3.4 Primary and Secondary Endpoints

3.4.1 Safety Endpoints

The primary safety endpoints are, among the first 24 patients treated for each study Stage (1 & 2):

- RLT.
- Sudden or unexpected deaths related to SL-701 or, in Stage 2, SL-701 in combination with bevacizumab.

Secondary safety endpoints in all enrolled patients will be AEs and SAEs, physical examinations, vital sign and weight measurements, clinical laboratory evaluations (hematology, serum chemistry, coagulation parameters, urinalysis) and reasons for discontinuation.

3.4.2 Efficacy Endpoints

Primary efficacy endpoints include:

- OS-12, per Kaplan-Meier estimate.
- ORR: Tumor response on 2 consecutive MRI assessments ≥4 weeks apart judged by modified RANO criteria.

Secondary efficacy endpoints include:

- Duration of tumor response (modified RANO criteria) (Wen 2010) (see Appendix 14.2).
- PFS (modified RANO criteria).
- OS.
- Magnitude of immune response in PBMCs.
- Tumor response, duration of tumor response, and PFS, judged by RECIST (version 1.1) criteria (Eisenhauer 2009) (see Appendix 14.3).

Exploratory endpoints include:

- Correlation between measures of immunogenicity and anti-tumor efficacy.
- Correlation between anti-tumor efficacy and either presence of glioma associated antigen in or infiltration of GAA-specific T-cells into available post-vaccine tumor tissue.
- Comparison of response based measures as assessed by modified RANO criteria and RECIST and correlation between responses and OS.
- Correlation of pseudoprogression (as defined in Section 3.2.2.2) and prolonged OS.

4. STUDY TREATMENTS

4.1 Study Drug Dosage and Administration

In Stage 1, a complete dose of study drug consists of the administration of a sequence of 3 agents, SL-701 emulsion (SL-701 in Montanide®) SC injection, GM-CSF SC injection, and imiquimod topical cream, administered within a 5 minute time frame. Topical application of imiquimod cream at the injection site is repeated at 24 h after each SL-701 emulsion injection. Each patient will be treated with SC injections of SL-701 emulsion every 14 days initially for 12 doses, followed by administrations every 28 days until determination of PD, withdrawal of informed consent, unacceptable toxicity, or noncompliance. Administration parameters for SL-701 emulsion and the adjuvants, GM-CSF and imiquimod, are summarized in Table 6. Study site personnel and patients should be instructed to wash hands before and after imiquimod topical use. Before applying, the treatment area should be washed with mild soap and water and allowed to dry thoroughly (at least 10 minutes). The treatment area should not be bandaged or otherwise occluded. Specific instructions for treatment site preparation and designation is provided in the study reference manual.

Table 6: Study Drug Dosage and Administration: Stage 1

Agent and Dose	Preparation and Route of Administration	Schedule
SL-701 in Montanide®; 1.0 mL injection taken from 0.7 mL of SL-701 mixed at a 1:1 (v/v) ratio with 0.7 mL of Montanide®*	Preferred site of SC injection is in the right or left upper arms with intact draining axillary nodes, alternating locations between individual vaccination dates. In case participants do not possess intact axillary lymph nodes as the draining nodes, administration is in the upper thigh on the same side with intact inguinal lymph nodes. The injection site should be selected and the area cleaned with soap and water and then dried thoroughly for at least 10 minutes. A circle with a radius of 18 mm will be marked out with ink at the injection site prior to SC injection to serve as a guide for the GM-CSF injection and imiquimod application.	Day 1; Weeks 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 22, then every 4 weeks thereafter
GM-CSF 150 µg	GM-CSF should be administered as a SC injection immediately after SL-701 emulsion administration and within 1 cm from the center of the SL-701 emulsion injection site, prior to application of topical imiquimod.	Day of each SL-701 emulsion dose

Agent and Dose	Preparation and Route of Administration	Schedule
Imiquimod Cream, 5% supplied in 250 mg single-use packets	Immediately (within 5 minutes) following the administration of the SL-701 emulsion, approximately one-half packet (125 mg) of imiquimod cream will be applied topically on the injection site. Study site personnel and patients will be instructed to wash hands before and after imiquimod topical use. Patients will be provided with instructions for the application process for the imiquimod cream at 24 h at the SL-701 emulsion injection site and told not wash the area for 48 h after the SL-701 emulsion injection (24 h after the second imiquimod application).** The imiquimod cream should be rubbed in until the cream is no longer visible.	Day of each SL-701 emulsion dose and 24 h after each SL-701 emulsion dose

* A 1.0 mL dose of the emulsion contains 0.3 mg each of the MPS-380, MPS-381, and MPS-486 peptides and 0.2 mg of the MPS-199 peptide.

** In situations where the 24h topical imiquimod is not administered according to protocol schedule for reasons other than adverse events (ie, the patient forgets to apply at 24 h), the patient may apply imiquimod during an additional 24-hour period subsequent to the stipulated administration time. Subsequent to this 24 hour window, the imiquimod dose will be considered "missed" and should not be applied.

In study Stage 2, a complete dose of investigational treatment consists of the administration of a sequence of 2 agents, SL-701 emulsion injection and poly-ICLC (IM) injection, within an approximate 20 minute time frame. Each patient will be treated with SC injections of SL-701 emulsion (SL-701 in Montanide®) twice weekly for the initial 2 weeks (5 doses), every 7 days during the subsequent 2 weeks (Weeks 3 and 4 treatment doses), and subsequently every 14 days for the subsequent 9 doses (16 doses total during approximately 22 weeks), followed by administrations every 28 days until determination of PD, withdrawal of informed consent, unacceptable toxicity, or noncompliance.

Patients will also receive IV bevacizumab at a dose of 10 mg/kg body weight starting on Day 1 and approximately every 2 weeks thereafter. For patients receiving study therapy beyond Week 22, bevacizumab will continue to be administered every 2 weeks until determination of PD, withdrawal of informed consent, unacceptable toxicity, or noncompliance.

Administration parameters for SL-701 emulsion and the adjuvant poly-ICLC are summarized in Table 7.

Table 7: Study Drug Dosage and Administration: Stage 2

Agent and Dose	Preparation and Route of Administration	Schedule
SL-701 in Montanide®; 1.0 mL injection taken from 0.7 mL of SL-701 mixed at a 1:1 (v/v) ratio with 0.7 mL of Montanide®*	Preferred site of SC injection is in the right or left upper arms with intact draining axillary nodes, alternating locations between individual vaccination dates. In case participants do not possess intact axillary lymph nodes as the draining nodes, administration is in the upper thigh on the same side with intact inguinal lymph nodes. The injection site should be selected and the area cleaned with soap and water (or alcohol) and then dried thoroughly for at least 10 minutes.	Day 1, Days 4, 8 (Week 1), 11, Weeks 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 22, then every 4 weeks thereafter
Poly-ICLC 1.6 mg (1,600 μg)	Within 20 minutes following the administration of the SL-701 emulsion, poly-ICLC should be administered as an IM injection in the same extremity (within 3 cm whenever possible) as was administered the SL-701 (deltoid muscle, unless contraindicated).	Day of each SL-701 emulsion dose
Bevacizumab Solution for intravenous injection	Following the administration of SL-701 and poly-ICLC, bevacizumab will be administered IV at a dose of 10 mg/kg. Bevacizumab infusions may occur over 30, 60 or 90 minutes in accordance with institutional practices and guidelines.	Day 1, Weeks 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 22, then every 2 weeks thereafter

* A 1.0 mL dose of the emulsion contains 0.3 mg each of the MPS-380, MPS-381, and MPS-486 peptides and 0.2 mg of the MPS-199 peptide.

4.2 Allowed Concomitant Treatment

Concomitant systemic corticosteroids are to be avoided if medically feasible. If used, corticosteroid doses should be the minimum necessary for appropriate clinical management. Any patient requiring initiation or significant increase in corticosteroid dosing due to progressive neurologic signs or symptoms should undergo a rigorous evaluation for progressing GBM. Efforts should be made to taper off corticosteroids as quickly as possible in the absence of PD. Topical steroids may be used only for severe injection site reactions. Inhaled corticosteroids may be administered as needed. As appropriate, topical or systemic non-steroidal anti-inflammatory or antihistamines may be used as alternatives. Patients with a history of prior Hepatitis B infection with evidence of immunity (ie, positive hepatitis B surface antibody [HBsAb]) should be treated with appropriate anti-viral therapy (ie, lamivudine, adefovir, or similar anti-viral agents) for the duration of investigational therapy.

All concomitant medications will be recorded on the electronic case report form (eCRF). The concomitant medication documentation for sexually active females of childbearing potential and sexually active males should support contraceptive usage, as applicable.

4.3 Prohibited Medications and Restrictions

Therapies including agents administered primarily for anti-tumor intent, including chemotherapy, bevacizumab (or other VEGF/VEGF receptor [VEGFR]-directed agent)s, or investigational anticancer agents are prohibited during participation in the study.

4.4 Assessment of Patient Compliance

On study drug administration days, patients will receive a paper diary (imiquimod diary) to remind them how to apply imiquimod 24 h after the SL-701 emulsion injection and to document their imiquimod use. After Day 1, study staff will collect these diaries and unused portion of the imiquimod packet at each study visit and at the End of Treatment visit.

4.5 Study Drug Description

During Stage 1, a complete dose of study drug consists of the administration of a sequence of 3 agents, SL-701 emulsion injection, GM-CSF injection and imiquimod topical cream, within a 5-minute time frame; topical application of imiquimod cream at the injection site is repeated at 24 h after each SL-701 emulsion injection.

During Stage 2, a complete dose of investigational treatment consists of the administration of a sequence of 2 agents, SL-701 emulsion injection and poly-ICLC (IM) injection, within an approximate 20-minute time frame. Patients will also receive IV bevacizumab; the bevacizumab infusion should occur following the administration of the other agents.

4.5.1 SL-701 Emulsion (Stages 1 and 2)

SL-701 consists of HLA-A2 restricted epitope peptides, MPS-380 (IL-13Rα2$_{345\text{-}353:1A9V}$), MPS-381 (EphA2$_{883\text{-}891}$), and MPS-486 (Survivin$_{95\text{-}104:3M}$), derived from 3 antigens that are overexpressed by glioma relative to normal tissues. SL-701 also includes MPS-199, a peptide that functions as a helper T-cell epitope derived from the TT, Tet$_{A830}$. Each vial of SL-701 contains each of the HLA peptides (MPS-380, MPS-381, and MPS-486) at a concentration of 0.6 mg/mL and contains the TT peptide MPS-199 at a concentration of 0.4 mg/mL. Please refer to Sections 1.2 and 1.3 regarding preliminary clinical experience with similar GAA peptide vaccines.

Montanide® (Montanide ISA 51 VG) is an oil-based adjuvant (containing a surfactant system) that is mixed 1:1 with SL-701 immediately before drug administration. Each emulsion dose delivered to the patient nominally will contain 0.3 mg of each of the HLA peptides and 0.2 mg of the tetanus toxoid peptide.

4.5.2 GM-CSF (Stage 1)

GM-CSF (LEUKINE, sargramostim) is a yeast-expressed recombinant human granulocyte-macrophage colony stimulating factor (rhu-GM-CSF). GM-CSF is a hematopoietic growth factor that stimulates proliferation and differentiation of hematopoetic progenitor cells. GM-CSF is approved by the US FDA following induction chemotherapy in acute myelogenous leukemia, for use in mobilization and following transplantation of autologous peripheral blood progenitor cells, for use in myeloid reconstitution after autologous or allogeneic bone marrow transplantation, and for use in bone marrow transplantation failure or engraftment delay. GM-CSF has been used experimentally in the development of cancer vaccines. Approved routes of GM-CSF administration are daily IV infusion or SC injection, with daily regimens of up to 14 days (or longer in some instances) administered in the pivotal studies.

In the pivotal studies evaluating GM-CSF, the majority of AEs observed did not occur at higher frequency in patients receiving GM-CSF versus those receiving placebo. AEs occurring at higher frequency in patients receiving GM-CSF infusion included fluid retention (peripheral edema, pleural effusion and pericardial infusion, without evidence of capillary leak syndrome), occasional dyspnea or

other respiratory symptoms (predominantly in patients with underlying lung disease), cardiac arrhythmia (predominantly in patients with a previous history of cardiac arrhythmia, reversible on discontinuation of GM-CSF), and increases in serum creatinine, or bilirubin and hepatic enzymes (transient and reversible, not observed at higher frequency in placebo-controlled clinical studies) (GM-CSF United States Package Insert).

4.5.3 Imiquimod Cream, 5% (Stage 1)

Imiquimod cream, 5% (ALDARA) is a topical immune response modifier approved by the US FDA for the treatment of actinic keratosis (AK), primary superficial basal cell carcinoma (sBCC), and external genital and perianal warts/condyloma acuminata (EGW). Approved regimens include topical application 2X/week (AK), 3X/week (EGW) and 5X/week (sBCC). Imiquimod is approved only for topical administration.

In controlled clinical studies, local skin and application site reactions were the most frequently reported adverse reactions, characterized as: itching, burning, erythema, flaking/scaling/dryness, scabbing/crusting, edema, induration, excoriation, erosion and ulceration. Severe local inflammatory reactions have been reported including skin weeping and erosion (which in some instances required dose interruptions in the pivotal studies evaluating 2×/week, 3×/week and 5×/week administration regimens). Flu-like systemic signs and symptoms have also been reported, including malaise, fever, nausea, myalgias, and rigors. Fatigue, fever and headache were reported in >1% of patients in pivotal studies, and at a higher frequency in patients receiving imiquimod (versus vehicle alone) (Imiquimod. United States Package Insert).

4.5.4 Poly-ICLC (Stage 2)

Poly-ICLC (polyinosinic-polycytidylic acid stabilized with polylysine and carboxymethyl cellulose) is a dsRNA that has been evaluated in multiple clinical cancer studies including pediatric and adult gliomas, in both treatment-naïve and recurrent settings, both as a monotherapy and in conjunction with other therapeutic modalities including radiation therapy. It is not licensed for commercial use in the US. Poly-ICLC was co-administered with GAA vaccine in 4 of 5 prior investigator-sponsored studies (schedules included both twice-weekly administration and every-3-week administration), and prior combination therapy was generally safe and well tolerated. The most common AEs observed in prior studies evaluating poly-ICLC were injection site reactions (discomfort, soreness, pain) which were predominantly mild and transient. Flu-like symptoms, including fever, fatigue, malaise, myalgias, arthralgia, chills/rigors and headache, have also been identified frequently, and were also predominantly mild and transient, although infrequent incidences of Grade 3 events have been reported. Leukopenia, including lymphopenia and neutropenia, have also been observed infrequently, including infrequent Grade 3 leukopenia. Increased transaminases (including infrequent Grade 3 elevations) have also been described. The majority of AEs identified in studies evaluating poly-ICLC have been mild and largely transient, with infrequent Grade 3 level events. In studies in which multiple doses (within the 10-50 µg/kg range) have been evaluated, dose-limiting toxicities have not been identified (Salazar 1996; Okada 2011; Butowski 2009a; Butowski 2009b; Hartman 2014).

4.5.5 Bevacizumab (Stage 2)

Bevacizumab (Avastin) is an anti-angiogenic monoclonal antibody directed against vascular endothelial growth factor (VEGF-A) and was initially approved in the US in 2004 for the treatment of colorectal cancer. Bevacizumab is currently indicated in metastatic colorectal cancer, non-squamous non-small cell

lung cancer, renal cancer, cervical cancer, ovarian cancer, and glioblastoma. In the neoplasia other than glioblastoma, bevacizumab is approved for use in conjunction with other anticancer agents (interferon-alpha in renal cancer, chemotherapy agents/combinations in the other diseases). Bevacizumab is approved in glioblastoma as a single agent for adult patients with PD following prior therapy, based on improvement in ORR in randomized studies. Side effects associated with bevacizumab include gastrointestinal perforations and fistulae, non-gastrointestinal fistulae, surgery and wound-healing complications, hemorrhage (ranging from frequent low-grade epistaxis to serious/fatal bleeding events), arterial thromboembolic events (mostly identified in patients receiving bevacizumab in combination with chemotherapy regimens, in patients with a history of prior arterial thromboembolism, diabetes, or age 65 or older), venous thromboembolic events, hypertension, posterior reversible encephalopathy syndrome (reported in fewer than 0.5% of patients enrolled in clinical studies), proteinuria (including nephrotic syndrome, reported in fewer than 1% of patients enrolled in clinical studies), infusion related reactions, and ovarian failure (in premenopausal women in combination with chemotherapy regimens). Although adequate studies evaluating bevacizumab in pregnancy have not been performed, this agent and other angiogenesis inhibitors have been shown to be teratogenic in animal studies; bevacizumab is classified as Pregnancy category C (Avastin Package Insert 5/2015).

4.6 Study Drug Packaging and Storage

SL-701 vials, packaged into labeled single vial cartons, will be shipped to sites frozen (-20°C). SL-701 cartons should be unpacked, counted, inspected for damage and registered in the Interactive Response Technology (IRT) system prior to placing in frozen storage (-20°C) at the clinical site. If a temperature excursion has occurred, register this event in the IRT System and do not use the product until directed to do so by the Sponsor. For additional handling and drug preparation instructions, please see the study pharmacy manual.

Montanide ISA 51 VG, packed in 10 vial cartons bearing a clinical label, will be shipped to sites controlled ambient temperature (15 - 25°C). Montanide® cartons should be unpacked, counted, inspected for damage and registered in the IRT system prior to storage at the clinical site. For additional handling and drug preparation instructions, please see the study pharmacy manual.

Leukine, 250µg (GM-CSF; Stage 1), packed in commercial 5 vial cartons bearing a clinical label, will be shipped to sites refrigerated (2 - 8°C). Leukine cartons should be unpacked, counted, inspected for damage and registered in the IRT system prior to placing in refrigerated storage at the clinical site. If a temperature excursion has occurred, register this event in the IRT System and do not use the product until directed to do so by the Sponsor. For additional handling and drug preparation instructions, please see the study pharmacy manual.

Imiquimod 5% cream packets (Stage 1), packed into 3 packet cartons, will be shipped to sites controlled ambient temperature (15 - 25°C). Imiquimod cartons should be unpacked, counted, inspected for damage and registered in the IRT system prior to storage at the clinical site. For additional handling and drug preparation instructions, please see the study pharmacy manual.

Poly-ICLC (Hiltonol; Stage 2), packaged into labeled single vial cartons, will be shipped to sites refrigerated (2 - 8°C). Poly-ICLC cartons should be unpacked, counted, inspected for damage and registered in the IRT system prior to placing in refrigerated storage at the clinical site. If a temperature excursion has occurred, register this event in the IRT System and do not use the product until directed to

do so by the Sponsor. For additional handling and drug preparation instructions, please see the study pharmacy manual.

Bevacizumab will be prescribed, prepared, and administered by means of standard pharmacy and institutional procedures.

4.7 Study Drug Accountability

The pharmacy will maintain accurate records of receipt of all test articles, including dates of receipt. In addition, accurate records will be kept regarding when and how much test article is dispensed and used for each patient in the study. All drug dispensing must be tracked in the IRT system to ensure accurate site inventory levels and the generation of resupply orders. Imiquimod dispensed to patients for use outside the clinic will be tracked, and patients will be asked to return any unused imiquimod to the clinic at each visit. Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all study drug will be reconciled and retained or destroyed according to applicable state and federal regulations.

All study drug must be kept in a secure location with access restricted to only necessary study site personnel and hospital pharmacist.

5. PATIENT ENROLLMENT

Patients must have shown unequivocal evidence of either a first tumor recurrence or progression during or following the initial treatment regimen prior to enrollment in this study, evidenced by MRI or CT. Please consult Section 6.1 and Section 6.2 concerning the timing and sequence of events beginning with consent for protocol evaluation and leading up to initial treatment with investigational therapy. The pre-treatment (ie, baseline) MRI or CT should be performed within 14 days prior to start of dosing with study drug. The dose of any corticosteroid must be stable or decreasing for at least 5 days prior to the scan. If the MRI or CT scan demonstrating recurrent or PD was obtained >14 days prior to the start of dosing with study treatment, a new baseline scan must be performed. Subsequent tumor response assessments will be performed every 8 weeks (± 7 days) thereafter until the Investigator determines there is evidence of PD using modified RANO response criteria (Wen 2010) (see Appendix 14.2). Patients who are evaluable for objective response will also be followed for DR, and all treated patients will be followed for OS and PFS until assessment of the primary objectives is completed.

5.1 Inclusion Criteria

To be enrolled in this study, patients must meet the following criteria during the Screening period (see Table 4 (Stage 1) and Table 5 (Stage 2), Study Event Schedule):

1. 18 years of age or older.
2. Histologically confirmed GBM or WHO Grade IV variants (gliosarcoma, glioblastoma with oligodendroglial features, or giant cell glioblastoma).
3. Unequivocal evidence of a first tumor recurrence or progression on the initial treatment regimen (prior to enrollment on this study), consisting of surgical intervention (biopsy and/or resection), radiation, and TMZ chemotherapy, as assessed by MRI or CT scan of the brain with and without contrast within 14 days prior to the start of SL-701. If receiving corticosteroids, the dose must be stable or decreasing for at least 5 days prior to the scan.

Patients unable to undergo MRI because of non-compatible devices can be enrolled, provided CT scans are obtained and are of sufficient quality. Patients without non-compatible devices may not have CT scans performed to meet this requirement. For each patient, the same imaging technique should be performed throughout the study for purposes of assessing tumor response or PD.

4. For patients who have undergone resection of recurrent or progressive tumor prior to study enrollment, the following conditions must apply:
   - Recovery from the effects of surgery.
   - Residual disease following resection of recurrent tumor is not mandated for eligibility into the study. To best assess the extent of residual disease post-operatively, an MRI should be performed:
     - No later than 96 h in the immediate post-operative period; or
     - At least 4 weeks post-craniotomy (7 days for stereotactic biopsy), within 14 days prior to the start of SL-701, and on a corticosteroid dosage that has been stable or decreasing for at least 5 days.
5. Patients who have not had resection of recurrent or PD must have measurable disease.
6. At least 56 of the approximately 76 patients treated must have measurable disease, defined as at least one, contrast-enhancing lesion measuring at least 1 cm in 2 planes (axial, coronal, or sagittal).
7. No evidence of hemorrhage on the baseline MRI or CT scan other than those that are ≤Grade1 and either post-operative or stable on at least 2 consecutive scans.
8. Recovery from prior therapy toxicity, defined as resolution of all treatment-related AEs to ≤Grade 1 or pre-treatment baseline (except alopecia and lymphopenia).
9. At least 12 weeks from prior radiotherapy to the start of SL-701 unless there is new enhancement outside of the radiation field or unequivocal histopathologic evidence of recurrent tumor subsequent to radiotherapy.
10. No chemotherapy or investigational agent for at least 3 weeks prior to the start of SL-701.
11. HLA-A2 positive.
12. A tumor tissue sample is provided for immunohistochemical analysis of relevant antigens, immune markers and potential prognostic factors. Preferably a paraffin block or 10-12 unstained slides will be submitted prior to study entry. Patients for whom tumor samples are unavailable or inadequate are permitted to participate in the study; however, the absence of available/adequate tumor specimen must be documented.
13. KPS score ≥70%.
14. Adequate organ function, including the following:
    - ANC ≥1,000/μL, platelets ≥100,000/μL.

- Serum creatinine ≤1.5 × the ULN.
- Bilirubin ≤1.5 × ULN.
- ALT and AST ≤2.5 × ULN.

15. Women of childbearing potential must have a negative serum or urine pregnancy test within 3 days prior to the start of SL-701 treatment.
16. Female patients of childbearing potential and sexually active male patients must agree to use an acceptable form of contraception for heterosexual activity (ie, oral contraceptives, double-barrier methods, hormonal injectable, transdermal, or implanted contraceptives, tubal ligation, or vasectomy of their sexual partner(s) for >40 days before Screening, during the study, and for 60 days after the last dose of study drug. Men should not donate semen during the study and for 60 days after the last dose of study drug.
17. Female patients without childbearing potential (spontaneous amenorrhea for >12 months or surgically sterilized by tubal ligation, hysterectomy, or bilateral oophorectomy >6 months before Screening) are eligible for inclusion without contraceptive use restriction.
18. Able and willing to comply with protocol requirements, in the opinion of the Investigator.
19. A written and voluntarily signed informed consent must be obtained from the patient or legally authorized representative, in accordance with local regulations, before the initiation of any study-related procedures. The patient or legally authorized representative must be able to read and understand the ICF.

5.2 Exclusion Criteria

Potential patients who meet any of the following criteria at Screening will be excluded from the study:

1. Prior cancer chemotherapy, bevacizumab (or other VEGF/VEGFR-directed agent), or an investigational agent for recurrent/progressive GBM or prior bevacizumab as part of initial therapy (prior chemotherapy or investigational agents are permitted as part of initial therapy; VEGF/VEGFR-directed agents are not permitted).
2. A contrast-enhancing brain tumor that is any of the following:
   - Multi-focal (defined as 2 separate areas of contrast enhancement measuring at least 1 cm in 2 planes that are not contiguous on either fluid-attenuated inversion recovery [FLAIR] or T2 sequences);
   - Associated with either diffuse subependymal or leptomeningeal dissemination; or
   - ≥4 cm in any dimension.
3. Requirement of systemic corticosteroid therapy >4 mg/day of dexamethasone or equivalent or requirement of increasing dose of systemic corticosteroids during the 7 days prior to the start of SL-701 treatment.
4. Surgical resection or major surgical procedure within 4 weeks prior to the start of SL-701, or stereotactic biopsy within 7 days prior to the start of SL-701.

5. Radiation therapy, local therapy (except for surgical re-resection), or systemic therapy following first recurrence or PD. Excluded local therapies following first recurrence/PD include stereotactic radiation boost, implantation of carmustine, biodegradable wafers (Gliadel), intratumoral or convection-enhanced delivery administered agents, etc.
6. Active infection requiring IV antibiotics.
7. History of cancer (other than GBM) within the past 2 years that has substantial metastatic or local recurrence potential and could negatively impact survival and/or potentially confound tumor response assessments within this study.
8. Clinically significant cardiovascular disease (eg, uncontrolled or any New York Heart Association Class 3 or 4 congestive heart failure, uncontrolled angina, history of myocardial infarction or stroke within 6 months of study entry, uncontrolled hypertension or clinically significant arrhythmias not controlled by medication).
9. Known immunosuppressive disease or active systemic autoimmune disease such as systemic lupus erythematosus, human immunodeficiency virus infection, active or chronic Hepatitis B or Hepatitis C, or has taken an immunosuppressive agent within 4 weeks prior to the start of SL-701 treatment. Patients with vitiligo, type 1 diabetes mellitus, hypothyroidism due to autoimmune condition only requiring hormone replacement therapy, psoriasis not requiring systemic therapy, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
10. Any condition that in the Investigator's opinion makes the patient unsuitable for study participation.
11. Requires therapeutic anticoagulation with warfarin at baseline; patients must be off warfarin or warfarin-derivative anti-coagulants for at least 7 days prior to starting study drug; however, therapeutic or prophylactic therapy with low-molecular weight heparin is allowed.
12. Has history of known coagulopathy that increases risk of bleeding or a history of clinically significant hemorrhage within 12 months of start of study drug.
13. Has evidence of intratumoral or peritumoral hemorrhage on baseline MRI scan other than those that are ≤Grade 1 and either post-operative or stable on at least 2 consecutive MRI scans
14. Has gastrointestinal bleeding or any other hemorrhage/bleeding event National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) >Grade 3 within 6 months of start of study drug.

5.3 Postponement of Investigational Regimen

In the setting of Grade 3 or higher laboratory abnormalities that were not present prior to initiation of investigational therapy, investigational therapy may be postponed for up to 2 weeks pending investigation of the abnormalities and appropriate supportive measures. In select circumstances, patients may receive treatment in the setting of persistent Grade 3 laboratory abnormalities, provided that the Investigator determines the abnormalities to be of limited clinical importance or not related to study therapy, and pending discussion with the Medical Monitor.

5.4 Modification of Investigational Regimen

In select circumstances, the investigational regimen may be modified in the setting of specific adverse events. No dose reduction for any of the treatment components is permitted. If SL-701 is discontinued for any reason, the imiquimod (Stage 1), GM-CSF (Stage 1), and poly-ICLC (Stage 2) adjuvants will be discontinued. SL-701 may be continued with discontinuation of either imiquimod, GM-CSF or poly-ICLC under the following circumstances:

5.4.1 Adverse Events Not Meeting the Definition of RLT

In the setting of a ≥Grade 3 skin (injection site) reaction lasting <7 days (at ≥Grade 3) or <Grade 3 skin (injection site) reaction that recurs and either results in treatment delay or substantial patient discomfort in the opinion of the Investigator, imiquimod (during Stage 1) or poly-ICLC (during Stage 2) may be withheld ("skipped") or discontinued and SL-701 (and GM-CSF [Stage 1]) continued. Any such modification should be discussed with the Medical Monitor and/or Investigator, and may be evaluated as a *potential* RLT during safety reviews/IDMC assessments.

In the setting of constitutional symptoms (including fatigue, fever, malaise, myalgia, edema [non-cerebral]) that do not meet the criteria for RLT but represent substantial patient discomfort and are at least possibly related to investigational therapy in the opinion of the Investigator (ie, ≥Grade 3 lasting ≤48 hours, or persistent <Grade 3, imiquimod (during Stage 1) or poly-ICLC (during Stage 2) may be withheld ("skipped") or discontinued and SL-701 (and GM-CSF [Stage 1]) continued. Any such modification should be discussed with the Medical Monitor and/or Investigator, and may be evaluated as a *potential* RLT during safety reviews/IDMC assessments.

In the setting of fluid retention (ie, ascites, pleural effusion) or dyspnea not meeting the criteria for RLT but representing substantial patient discomfort in the opinion of the Investigator, GM-CSF (during Stage 1) may be withheld ("skipped") or discontinued and SL-701 (and imiquimod) continued. Any such modification should be discussed with the Medical Monitor and/or Investigator, and may be evaluated as a *potential* RLT during safety reviews/IDMC assessments.

In Stage 2, in the setting of Grade 3 or higher transaminase elevations or leukopenia not meeting the criteria for RLT, poly-ICLC may be withheld ("skipped") or discontinued and SL-701 (and bevacizumab) continued. Any such modification should be discussed with the Medical Monitor and/or Investigator, and may be evaluated as a *potential* RLT during safety reviews/IDMC assessments.

5.4.2 RLT and RLT-level Adverse Events

In the setting of a Grade ≥ 3 skin (injection site) reaction lasting ≥ 7 days (at Grade ≥ 3); imiquimod (during Stage 1) or poly-ICLC (during Stage 2) may be discontinued and SL-701 (with GM-CSF [Stage 1]) continued pending adequate resolution (Grade 1 or less) or the reaction. If the Grade ≥ 3 reaction recurs then SL-701 (and GM-CSF) will be discontinued.

In the setting of Grade ≥ 3 constitutional symptoms (including fatigue, fever, malaise, myalgia, edema [non-cerebral]) that persist for > 48 hours, imiquimod (during Stage 1) or poly-ICLC (during Stage 2) may be discontinued and SL-701 (with GM-CSF [Stage 1]) continued pending adequate resolution (Grade 1 or less). If a Grade ≥ 3 event recurs then SL-701 (and GM-CSF) will be discontinued.

During Study Stage 2, any event resulting in the permanent withdrawal of SL-701 will also warrant withdrawal of poly-ICLC. Bevacizumab may be continued following permanent cessation of SL-701 (and poly-ICLC).

5.4.3 Modification of Bevacizumab

Bevacizumab should not be dose-reduced (or increased) during the course of study therapy. In specific settings, bevacizumab should be withheld pending either further evaluation of adverse events or resolution. Such settings include severe hypertension not adequately controlled by medical management, proteinuria greater than or equal to 2g/24 hours, hemoptysis of ≥½ teaspoon (2.5 cc) of blood, or other Grade 1-2 adverse events attributed to bevacizumab that are burdensome to the patient and for which a temporary interruption of bevacizumab may enable improvement, in the opinion of the Investigator. For full dosing recommendations, warnings and precautions, please consult the bevacizumab package insert (Avastin Package Insert 5/2015).

Patients for whom bevacizumab has withheld ("skipped") may continue to receive SL-701 (and poly-ICLC) during Stage 2 of the study.

5.5 Patient Withdrawal

5.5.1 Reasons for Withdrawal

Patients will be informed that they are free to withdraw from the study at any time and for any reason. Patients will be discontinued from the study if any of the following occur:

- In the opinion of the Investigator, it is not in the best interest of the patient to continue the study.
- There is a change in compliance with an inclusion/exclusion criterion that is clinically relevant and affects patient safety.
- The patient takes a concomitant medication that might affect patient safety or study assessments/objectives.
- The patient develops RLT as defined in Section 3.2.2, or an RLT-level toxicity (for patients receiving ongoing therapy beyond the initial 12 doses of investigational therapy), other than the specific situations defined in Section 5.4 (Modification of Investigational Regimen).
- The patient develops a persistent toxicity that does not meet the criteria for RLT, but that is nonetheless intolerable in the opinion of the patient and/or the Investigator.
- Unequivocal evidence of PD as detailed in Section 3.2.2.2 and Section 3.3 (in situations where potential pseudoprogression is under clinical/radiographic evaluation, investigational therapy may be administered or postponed as detailed in these sections).

Patient participation in the study may be stopped at any time at the discretion of the Investigator or at the request of the Sponsor. Discontinuation procedures are described in Section 5.5.3.

5.5.2 Withdrawal of Bevacizumab

Bevacizumab therapy should be permanently discontinued in the setting of gastrointestinal perforations, fistulae (gastrointestinal or non-gastrointestinal), necrotizing fasciitis, severe hemorrhage, severe arteriothromboembolic events, life threatening venous thromboembolic events (including pulmonary

embolism), hypertensive crisis or hypertensive encephalopathy, posterior reversible encephalopathy syndrome, nephrotic syndrome, or severe infusion related reaction. For comprehensive warnings and precautions, please consult the bevacizumab package insert (Avastin Package Insert 5/2015).

Patients for whom bevacizumab has been discontinued may continue to receive SL-701 (and poly-ICLC) during Stage 2 of the study.

5.5.3 Handling of Withdrawals

Patients who discontinue SL-701 should return for a final visit, consisting of all tests and procedures listed for the End of Treatment visit in Table 4 (Stage 1) and Table 5 (Stage 2). If the patient is in CR/PR at the time of discontinuation, tumor assessments should continue to be performed as described in Section 7.1 until, in the judgment of the Investigator, there is evidence of relapsed or progressive disease. In addition, patients should be followed for a minimum of 30 days after the last dose of study drug for AEs. Beyond this safety evaluation period, patients should be asked if they are willing to continue follow-up for survival and documentation of subsequent salvage therapy.

If the patient discontinues study drug and also withdraws consent for collection of future information, no further evaluations should be performed and no additional data should be collected as part of the study. The Sponsor will only retain and use any data collected before withdrawal of consent.

Patients who fail to appear for a study visit within 7 days of the scheduled visit will be contacted directly by the study site personnel. If a visit is missed, a minimum of 2 documented telephone calls to the patient should be made over the course of at least 2 weeks. If the study site personnel receive no response, they should send a certified letter requesting that the patient contact the study site regarding his or her status in the study. If a patient does not return for the final visit, and the appropriate permission has been obtained, the Investigator may obtain a verbal report on the patient's health status from the patient's local health care provider.

5.5.4 Replacements

At the discretion of the Sponsor, additional patients may be enrolled to supplement patient data compromised due to premature study dropout or other reasons. Only patients who have enrolled in the study and have withdrawn or been designated as a screen failure prior to receiving the first dose of study drug will be replaced. If dosed, patients who withdraw will not be replaced.

5.5.5 Termination of Study by Sponsor

Although the Sponsor has every intention of completing the study, it reserves the right to discontinue the study at any time for clinical or administrative reasons or if required by the FDA. Both the Sponsor and the contract research organization (CRO) Medical Monitors will review the safety of the study drug regimen throughout the study. The study may be halted at any time for safety concerns.

6. STUDY VISITS

All study visits, assessments, and procedures involving study patients will be performed at a Sponsor- approved investigative site, and assessments and procedures will be performed by study personnel with the supervision of an Investigator. Study drug will be administered only at an approved investigative site.

Study drug administration (including adjuvant administration) will be the last procedure performed during each study visit at which study drug is scheduled to be administered. The dosing date and times for all 3 agents must be recorded.

6.1 Screening

The following will be done after the patient or legally authorized representative provides informed consent, with measurements and results recorded in the eCRF:

- Record medications taken in the 28 days before Screening.
- Verify and document satisfaction of entry criteria.
  - Local laboratory results obtained within a 14-day screening period prior to the first dose of study drug may be used to verify entry criteria.
  - Laboratory evaluation of HLA status may be obtained within a 28-day screening period prior to the first dose of study drug.
  - If patient has evaluable but not measurable disease, confirm enrollment with Sponsor (at least 80 of the 100 patients treated must have measurable disease).
- Record medical and surgical history.
- Record all current medications.
- Conduct complete physical examination and measure height.
- Perform serum or urine pregnancy test for women of childbearing potential.
- Record vital sign measurements and weight.
- Obtain hematology, serum chemistry, blood coagulation, and urinalysis samples (the results of any test obtained within the 14-day screening period may be used for screening purposes).
- Perform MRI or CT scan. Retain as source document for the study.
- Perform objective tumor measurements/assessment by RECIST (version 1.1) (see Appendix 14.3) and modified RANO criteria (see Appendix 14.2). Document tumor evaluation.
- Evaluate KPS score (see Appendix 14.1).
- Tumor tissue submission, as available. If tumor tissue is collected and available following initiation of study therapy, or at any time point throughout the duration of the study, then a sample must be submitted for immunohistochemical analysis.

6.2 Day 1

Treatment must begin within 14 days of completing all screening procedures, immediately after treatment assignment and must begin within 24 h of the end of the Screening period. Day 1 procedures include:

- Record all concomitant medications.
- Record vital signs and weight.

- Obtain hematology, serum chemistry, blood coagulation, and urinalysis samples
- Perform phlebotomy for immune response studies and send blood to central laboratory
- Wash and dry dosing site with mild soap and water and allow to dry at least 10 minutes. Prepare and mark skin (18 mm radius circle) to designate treatment area. Specific treatment site preparation instructions are provided in the study reference manual.
- Administer first dose of SL-701 emulsion by SC injection.

Stage 1:

- Immediately following the injection of SL-701 emulsion, inject 150 µg GM-CSF within 1 cm of the center of the SL-701 emulsion injection site (Stage 1 only).
- Within 5 minutes after injection of SL-701 emulsion, study personnel will apply one-half packet of imiquimod cream to an area within 18 mm of the SL-701 emulsion injection site (Stage 1 only).
- Instruct patient not to wash the area within 18 mm of the SL-701 emulsion injection site for 48 h after the time of the SL-701 emulsion injection (Stage 1 only).
- Instruct patient to apply one-half packet of imiquimod cream to the area within 18 mm of the SL-701 emulsion injection site, 24 h after the SL-701 emulsion injection. Patients will be given a packet of imiquimod Cream 5% to take home. Instruct patient that in the setting of a severe skin or injection site reaction occurring within 24 hours after the SL-701 emulsion injection, to remove the imiquimod by washing with mild soap and water, and to **not** administer the additional half-packet of imiquimod 24 hours subsequent to the SL-701 emulsion injection (non-occlusive dressings such as cotton gauze may be used for imiquimod related skin [injection site] reactions) (Stage 1 only).
- Dispense patient imiquimod diary, and instruct patient in the use thereof. Remind patients to bring back unused packet of imiquimod on next study visit (Stage 1 only).
-

Stage 2:

- Within 20 minutes following the injection of SL-701 emulsion, inject 1,600 µg (1.6 mg) poly-ICLC IM in the same extremity (within 3 cm) as was administered the SL-701 injection (Stage 2 only).
- Administer IV bevacizumab at a dose of 10 mg/kg of body weight (infusion to be given over 30, 60 or 90 minutes in accordance with institutional practices and guidelines).

- Record any AEs since last visit.

6.3 Day 4, Day 8 (Week 1), Day 11, and Week 3 (Stage 2 only)

During the initial 2 weeks of study therapy (in Stage 2), SL-701 emulsion and adjuvant will administered twice per week. The Day 4 and Day 11 visits may be performed ± 1 day (ie, on either Days 3, 4, or 5 and on either Days 9, 10, or 11). The Day 8 (Week 1) visit should be done as closely as possible to a date 1

week after the Day 1 SL-701 emulsion administration (± 3 days is permitted). The following procedures will be performed at Study Days 4, 8 (Week 1), 11 and Week 3 with the results recorded in the eCRF:

- Record all concomitant medications.
- Record vital signs and weight.
- Obtain hematology and serum chemistry samples.
- Wash and dry dosing site with mild soap and water and allow to dry at least 10 minutes. Prepare and mark skin (18 mm radius circle) to designate treatment area. Specific treatment site preparation instructions are provided in the study reference manual.
- Administer dose of SL-701 emulsion by SC injection.

Stage 2:

- Within 20 minutes following the injection of SL-701 emulsion, inject 1,600 µg (1.6 mg) poly-ICLC IM in the same extremity (within 3 cm) as was administered the SL-701 injection (Stage 2 only).

- Record any AEs since last visit and status of unresolved AEs.

6.4 Weeks 2, 4, 6, 10, 12, 14, 18, 20, and 22

The Week 2 visit should be done as closely as possible to a date 2 weeks after the Day 1 SL-701 emulsion administration date (± 3 days is permitted). Study visits and assessments after the SL-701 emulsion administration at Week 2 should be done within a ± 3 day window adhering to the schedule in Table 4 (Stage 1) and Table 5 (Stage 2). The following procedures will be performed at Study Weeks 2, 4, 6, 10, 12, 14, 18, 20 and 22, with the results recorded in the eCRF:

- Record all concomitant medications.
- Physical examination (Weeks 4, 12 and 20).
- Record vital signs and weight.
- Obtain hematology, serum chemistry, blood coagulation, and urinalysis samples
- Perform phlebotomy for immune response studies and send blood to central laboratory (Weeks 4, and 12).
- Wash and dry dosing site with mild soap and water and allow to dry at least 10 minutes. Prepare and mark skin (18 mm radius circle) to designate treatment area. Specific treatment site preparation instructions are provided in the study reference manual.
- Administer dose of SL-701 emulsion by SC injection.

Stage 1:

- Immediately after injecting SL-701 emulsion, inject 150 µg GM-CSF within 1 cm of the center of the SL-701 emulsion injection site (Stage 1 only).

- Within 5 minutes after injecting SL-701 emulsion, study personnel will apply one-half packet of imiquimod cream to an area within 18 mm of the SL-701 emulsion injection site (Stage 1 only).
- Instruct patient not to wash the area within 18 mm of the SL-701 emulsion injection site for 48 h after the time of the SL-701 emulsion injection (Stage 1 only).
- Instruct patient to apply one-half packet of imiquimod cream to the area within 18 mm of the SL-701 emulsion injection site, 24 h after the SL-701 emulsion injection. Patients will be given a packet of imiquimod Cream 5% to take home. Instruct patient that in the setting of a severe skin or injection site reaction occurring within 24 hours after the SL-701 emulsion injection, to remove the imiquimod by washing with mild soap and water, and to **not** administer the additional half-packet of imiquimod 24 hours subsequent to the SL-701 emulsion injection (non-occlusive dressings such as cotton gauze may be used for imiquimod related skin [injection site] reactions) (Stage 1 only).
- Collect patient imiquimod diary and remainder of unused imiquimod (Stage 1 only).
- Dispense patient imiquimod diary, and instruct patient in the use thereof. Remind patients to bring back unused packet of imiquimod on next study visit (Stage 1 only).

Stage 2:

- Within 20 minutes following the injection of SL-701 emulsion, inject 1,600 µg (1.6 mg) poly-ICLC IM in the same extremity (within 3 cm) as was administered the SL-701 injection (Stage 2 only).
- Administer IV bevacizumab at a dose of 10 mg/kg of body weight (infusion to be given over 30, 60 or 90 minutes in accordance with institutional practices and guidelines).

- Record any AEs since last visit and status of unresolved AEs.

6.5 Weeks 8 and 16

The following procedures will be performed at Weeks 8 and 16, with the results recorded in the eCRF:

- Record all concomitant medications.
- Physical examination.
- Record vital signs and weight.
- Obtain hematology, serum chemistry, blood coagulation, and urinalysis samples.
- Perform phlebotomy for immune response studies and send blood to central laboratory.
- Perform clinical assessment for PD.
- Perform brain MRI or CT scan, depending on what type of scan was used to qualify the patient during Screening.
- Perform objective tumor response assessment using RECIST criteria, version 1.1 (see Appendix 14.3) and modified RANO criteria (see Appendix 14.2).

- Evaluate KPS score (see Appendix 14.1).
- Wash and dry dosing site with mild soap and water and allow to dry at least 10 minutes. Prepare and mark skin (18 mm radius circle) to designate treatment area. Specific treatment site preparation instructions are provided in the study reference manual.
- Administer dose of SL-701 emulsion by SC injection.

Stage 1:

- Immediately after injecting SL-701 emulsion, inject 150 µg GM-CSF within 1 cm of the center of the SL-701 emulsion injection site (Stage 1 only).
- Within 5 minutes after injecting SL-701 emulsion, study personnel will apply one-half packet of imiquimod cream to an area within 18 mm of the SL-701 emulsion injection site (Stage 1 only).
- Instruct patient not to wash the area within 18 mm of the SL-701 emulsion injection site for 48 h after the time of the SL-701 emulsion injection (Stage 1 only).
- Instruct patient to apply one-half packet of imiquimod cream to the area within 18 mm of the SL-701 emulsion injection site, 24 h after the SL-701 emulsion injection. Patients will be given a packet of imiquimod Cream 5% to take home. Instruct patient that in the setting of a severe skin or injection site reaction occurring within 24 hours after the SL-701 emulsion injection, to remove the imiquimod by washing with mild soap and water, and to **not** administer the additional half-packet of imiquimod 24 hours subsequent to the SL-701 emulsion injection (non-occlusive dressings such as cotton gauze may be used for imiquimod related skin [injection site] reactions) (Stage 1 only).
- Collect patient imiquimod diary and remainder of unused imiquimod (Stage 1 only).
- Dispense patient imiquimod diary, and instruct patient in the use thereof. Remind patients to bring back unused packet of imiquimod on next study visit (Stage 1 only).

Stage 2:

- Within 20 minutes following the injection of SL-701 emulsion, inject 1,600 µg (1.6 mg) poly-ICLC IM in the same extremity (within 3 cm) as was administered the SL-701 injection (Stage 2 only).
- Administer IV bevacizumab at a dose of 10 mg/kg of body weight (infusion to be given over 30, 60 or 90 minutes in accordance with institutional practices and guidelines).

- Record any AEs since last visit and status of unresolved AEs.

6.6 Week 24

The following procedures will be performed at Week 24, with the results recorded in the eCRF:

- Record all concomitant medications.
- Record vital signs and weight.

- Collect patient imiquimod diary and remainder of unused imiquimod (Stage 1 only).
- Perform phlebotomy for immune response studies and send blood to central laboratory.
- Perform clinical assessment for PD.
- Perform brain MRI or CT scan, depending on what type of scan was used to qualify the patient during Screening.
- Perform objective tumor response assessment using RECIST criteria, version 1.1 (see Appendix 14.3) and modified RANO criteria (see Appendix 14.2).
- Evaluate KPS score (see Appendix 14.1).
- Record any AEs since last visit and status of unresolved AEs.

6.7 Weeks 26 and 30

The following procedures will be performed at Weeks 26 and 30, (some evaluations are to be performed at only Week 26 or Week 30 as indicated below), with the results recorded in the eCRF:

- Record all concomitant medications
- Physical examination.
- Record vital signs and weight.
- Obtain hematology, serum chemistry, blood coagulation, and urinalysis samples.
- Evaluate KPS score (see Appendix 14.1; Week 26 only).
- Administer dose of SL-701 emulsion by SC injection.

Stage 1:

- Collect patient imiquimod diary and remainder of unused imiquimod (Week 30, Stage 1 only).
- Immediately after injecting SL-701 emulsion, inject 150 µg GM-CSF within 1 cm of the center of the SL-701 emulsion injection site (Stage 1 only).
- Within 5 minutes after injecting SL-701 emulsion, study personnel will apply one-half packet of imiquimod cream to an area within 18 mm of the SL-701 emulsion injection site (Stage 1 only).
- Instruct patient not to wash the area within 18 mm of the SL-701 emulsion injection site for 48 h after the time of the SL-701 emulsion injection (Stage 1 only).
- Instruct patient to apply one-half packet of imiquimod cream to the area within 18 mm of the SL-701 emulsion injection site, 24 h after the SL-701 emulsion injection. Patients will be given a packet of imiquimod Cream 5% to take home. Instruct patient that in the setting of a severe skin or injection site reaction occurring within 24 hours after the SL-701 emulsion injection, to remove the imiquimod by washing with mild soap and water, and to **not** administer the additional half-packet of imiquimod 24 hours subsequent to the SL-701

emulsion injection (non-occlusive dressings such as cotton gauze may be used for imiquimod related skin [injection site] reactions) (Stage 1 only).

- Dispense patient imiquimod diary, and instruct patient in the use thereof. Remind patients to bring back unused packet of imiquimod on next study visit (Stage 1 only).

Stage 2:

- Within 20 minutes following the injection of SL-701 emulsion, inject 1,600 µg (1.6 mg) poly-ICLC IM in the same extremity (within 3 cm) as was administered the SL-701 injection (Stage 2 only).
- Administer IV bevacizumab at a dose of 10 mg/kg of body weight (infusion to be given over 30, 60 or 90 minutes in accordance with institutional practices and guidelines).

- Record any AEs since last visit and status of unresolved AEs.

6.8 Weeks 28 and 32 (Stage 2 only)

In Stage 2, the following procedures will be performed at Weeks 28 and 32, with the results recorded in the eCRF:

- Record all concomitant medications
- Record vital signs and weight.
- Administer IV bevacizumab at a dose of 10 mg/kg of body weight (infusion to be given over 30, 60, or 90 minutes in accordance with institutional practices and guidelines.
- Record any AEs since last visit and status of unresolved AEs.

6.9 Week 34

The following procedures will be performed at Week 34, with the results recorded in the eCRF:

- Record all concomitant medications.
- Physical examination.
- Record vital signs and weight.
- Obtain hematology, serum chemistry, blood coagulation, and urinalysis samples.
- Perform phlebotomy for immune response studies and send blood to central laboratory.
- Perform clinical assessment for PD.
- Perform brain MRI or CT scan, depending on what type of scan was used to qualify the patient during Screening.
- Perform objective tumor response assessment using RECIST criteria, version 1.1 (see Appendix 14.3) and modified RANO criteria (see Appendix 14.2).
- Evaluate KPS score (see Appendix 14.1).

- Wash and dry dosing site with mild soap and water and allow to dry at least 10 minutes. Prepare and mark skin (18 mm radius circle) to designate treatment area. Specific treatment site preparation instructions are provided in the study reference manual.
- Administer dose of SL-701 emulsion by SC injection.

Stage 1:

- Collect patient imiquimod diary and remainder of unused imiquimod (Stage 1 only).
- Immediately after injecting SL-701 emulsion, inject 150 µg GM-CSF within 1 cm of the center of the SL-701 emulsion injection site (Stage 1 only).
- Within 5 minutes after injecting SL-701 emulsion, study personnel will apply one-half packet of imiquimod cream to an area within 18 mm of the SL-701 emulsion injection site (Stage 1 only).
- Instruct patient not to wash the area within 18 mm of the SL-701 emulsion injection site for 48 h after the time of the SL-701 emulsion injection (Stage 1 only).
- Instruct patient to apply one-half packet of imiquimod cream to the area within 18 mm of the SL-701 emulsion injection site, 24 h after the SL-701 emulsion injection. Patients will be given a packet of imiquimod Cream 5% to take home. Instruct patient that in the setting of a severe skin or injection site reaction occurring within 24 hours after the SL-701 emulsion injection, to remove the imiquimod by washing with mild soap and water, and to **not** administer the additional half-packet of imiquimod 24 hours subsequent to the SL-701 emulsion injection (non-occlusive dressings such as cotton gauze may be used for imiquimod related skin [injection site] reactions) (Stage 1 only).
- Dispense patient imiquimod diary, and instruct patient in the use thereof. Remind patients to bring back unused packet of imiquimod on next study visit (Stage 1 only).

Stage 2:

- Within 20 minutes following the injection of SL-701 emulsion, inject 1,600 µg (1.6 mg) poly-ICLC IM in the same extremity (within 3 cm) as was administered the SL-701 injection (Stage 2 only).
- Administer IV bevacizumab at a dose of 10 mg/kg of body weight (infusion to be given over 30, 60, or 90 minutes in accordance with institutional practices and guidelines).

- Record any AEs since last visit and status of unresolved AEs.

6.10 Subsequent to Week 34

The following assessments will be performed every 4 weeks unless otherwise stipulated, until the end of treatment visit, with the results recorded in the eCRF.

- Collect patient imiquimod diary and remainder of unused imiquimod (Stage 1 only).
- Record all concomitant medications.

- Physical examination.
- Record vital signs and weight.
- Obtain hematology, serum chemistry, blood coagulation, and urinalysis samples.
- Perform phlebotomy for immune response studies and send blood to central laboratory (every 8 weeks through Week 50; every 12 weeks thereafter and at end-of-treatment visit).
- Perform clinical assessment for PD (every 8 weeks though Week 50; every 12 weeks thereafter).
- Perform brain MRI or CT scan, depending on what type of scan was used to qualify the patient during Screening (every 8 weeks though Week 50; every 12 weeks thereafter).
- Perform objective tumor response assessment using RECIST criteria, version 1.1 (see Appendix 14.3) and modified RANO criteria (see Appendix 14.2; every 8 weeks though Week 50; every 12 weeks thereafter).
- Evaluate KPS score (see Appendix 14.1; every 8 weeks though Week 50; every 12 weeks thereafter).
- Wash and dry dosing site with mild soap and water and allow to dry at least 10 minutes. Prepare and mark skin (18 mm radius circle) to designate treatment area. Specific treatment site preparation instructions are provided in the study reference manual.
- Administer dose of SL-701 emulsion by SC injection.

Stage 1:

- Immediately after injecting SL-701 emulsion, inject 150 µg GM-CSF within 1 cm of the center of the SL-701 emulsion injection site (Stage 1 only).
- Within 5 minutes after injecting SL-701 emulsion, study personnel will apply one-half packet of imiquimod cream to an area within 18 mm of the SL-701 emulsion injection site (Stage 1 only).
- Instruct patient not to wash the area within 18 mm of the SL-701 emulsion injection site for 48 h after the time of the SL-701 emulsion injection (Stage 1 only).
- Instruct patient to apply one-half packet of imiquimod cream to the area within 18 mm of the SL-701 emulsion injection site, 24 h after the SL-701 emulsion injection. Patients will be given a packet of imiquimod Cream 5% to take home. Instruct patient that in the setting of a severe skin or injection site reaction occurring within 24 hours after the SL-701 emulsion injection, to remove the imiquimod by washing with mild soap and water, and to **not** administer the additional half-packet of imiquimod 24 hours subsequent to the SL-701 emulsion injection (non-occlusive dressings such as cotton gauze may be used for imiquimod related skin [injection] reactions) (Stage 1 only).
- Dispense patient imiquimod diary, and instruct patient in the use thereof. Remind patients to bring back unused packet of imiquimod on next study visit (Stage 1 only).

Stage 2:

- Within 20 minutes following the injection of SL-701 emulsion, inject 1,600 µg (1.6 mg) poly-ICLC IM in the same extremity (within 3 cm) as was administered the SL-701 injection (Stage 2 only).
- Administer IV bevacizumab at a dose of 10 mg/kg of body weight (infusion to be given over 30, 60, or 90 minutes in accordance with institutional practices and guidelines); bevacizumab should be administered **every 2 weeks** until PD or unacceptable toxicity.

- Record any AEs since last visit and status of unresolved AEs.

6.11 End of Treatment Visit

The End of Treatment Visit for each patient will occur approximately 14 days after determination that withdrawal from the study is necessary, either because of PD, RLT, or other reason initiated by either the Investigator or the patient. The visit at which the determination for study discontinuation is made is not the End of Treatment Visit, and should be recorded in the eCRF based on the study week (eg, Week 18), regardless of whether treatment is administered at that visit. The following procedures will be performed at the End of Treatment Visit:

- Record all concomitant medications.
- Perform physical examination
- Perform serum or urine pregnancy test in women of childbearing potential.
- Record vital signs and weight.
- Obtain hematology, serum chemistry, blood coagulation, and urinalysis samples.
- Collect patient imiquimod diary and remainder of unused imiquimod (Stage 1 only).
- Perform phlebotomy for immune response studies and send blood to central laboratory.
- Evaluate KPS score (see Appendix 14.1).
- Perform clinical assessment for PD.
- Record any AEs since last visit and status of unresolved AEs.

6.12 Telephone Call Follow-up 30 Days after Last Dose

Patients will receive a follow-up telephone call approximately 30 days after their last dose of study drug to assess their status, to check for AEs and concomitant medications, and to document any salvage therapy after their last dose of SL-701 emulsion. Site staff will remind women of childbearing potential and sexually active male patients to continue to use an acceptable form of contraception for heterosexual activity (ie, oral contraceptives, double barrier methods, hormonal injectable, transdermal, or implanted contraceptives, tubal ligation, or vasectomy of their sexual partner(s) for 60 days after the last dose of study drug. Men will be reminded that they should not donate semen during this same time period.

6.13 Telephone Call Follow-up Every 90 days after Last Dose

Study personnel will call each patient every approximately 90 days after the patient has received their last dose of study drug to determine patient survival status and to document any salvage therapy since the last dose of study drug.

7. STUDY ASSESSMENTS

The assessments in the following subsections will be done to collect data needed for this research study. It is expected that the Investigator and hospital staff will follow the medically accepted standard of care for GBM patients, and perform these assessments on the scheduled study visit days. The results of all study assessments are to be recorded promptly in the eCRF.

7.1 Tumor Response Assessment

The primary criteria for assessing tumor response will be the modified RANO criteria (Wen 2010) (see Appendix 14.2). RECIST (version 1.1) (see Appendix 14.3) will be secondary criteria (Eisenhauer 2009). The categories of response are: CR, PR, SD, and PD. A board certified radiologist will be responsible for the objective measurements and evaluations of each patient's MRI or CT scans. While each investigative site may use its own radiologist, it is desirable that a single radiologist be assigned to review all the scans for a single patient, and, ideally all the patients at a particular site. There will not be a central radiologist reviewing all scans, nor a team of radiologists reviewing all MRI or CT scans. Each Investigator will be responsible for integrating the radiology reports of the MRI or CT scans with the clinically assessed progress of each patient. Tumor response assessments will follow each MRI or CT scan within 7 days, and will be entered into the eCRF by each Investigator. MRI or CT scans will be performed according to the Study Event Schedule (Table 4 [Stage 1] and Table 5 [Stage 2]). As part of the RANO criteria assessment, information will be collected on the patient's clinical status (eg, stable, improved, or declining since the last assessment), functional neurological status using the KPS score and concomitant medications, including corticosteroid use.

The modified RANO criteria include an overall assessment of clinical deterioration that is based on the clinical and functional neurological status of the patient. The KPS score, a commonly used scale for rating a patient's capacity to function under the burden of his disease, will be used to provide consistency in this assessment across sites. The Investigator will record each patient's KPS score at each study visit. The KPS scale is found in Appendix 14.1.

7.2 Demographic Data/Medical History

Demographic data and a complete medical and surgical history will be collected at Screening. The medical history should include the past 2 years whenever possible. Data related to the current tumor under study should not be recorded in the medical history, but rather under signs and symptoms.

7.3 Prior Medications

All medications taken in the 28 days before Screening, including nonprescription medications, dietary supplements and the specific dose/schedule of any systemic corticosteroid agents, will be recorded.

7.4 Clinical Laboratory Tests

All clinical laboratory testing will be performed at local sites. The clinical laboratory test will be collected at Screening, on Day 1, at Weeks 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 26, 30, and 34, and then every 4 weeks after that date or at the End of Treatment visit. Tests to be performed include hematology, serum chemistry, coagulation parameters, and urinalysis as found in Table 4 (Stage 1) and Table 5 (Stage 2). A serum or urine pregnancy test will be performed in women of childbearing potential at Screening and at the End of Treatment visit. Laboratory tests may be performed either on the day of a treatment visit, or during the 3 days prior to a treatment visit (it should be noted that if a test is performed during the days prior to a treatment visit, the results should nonetheless be considered as part of the visit for the week at which the treatment is subsequently administered; for example a laboratory test performed 2 days prior to the Week 6 visit is technically conducted during the 5th week of study participation, but should be recorded as the "Week 6" laboratory assessment).

7.5 Vital Sign Measurements and Body Weight

Blood pressure, heart rate, respiratory rate, body temperature, and body weight measurements will be obtained at every study visit. Body weight will be measured in kg.

7.6 Physical Examination

A complete physical examination will be performed during Screening and at the End of Treatment visit. The examination will include the following body systems: general appearance; eyes, ears, nose and throat, head and neck; chest and lungs; cardiovascular; abdomen; musculoskeletal; lymphatic; dermatologic; neurologic; psychiatric; and extremities. Physical examinations will be conducted by a physician or health professional listed on the Form FDA 1572 and licensed to perform physical examinations. The physical examination at Screening will include a height measurement (cm). A directed physical examination involving any body systems for which abnormal findings were present during screening (or prior) examinations, and any systems determined relevant by the Investigator, will be conducted every 4 weeks, as indicated in Table 4 (Stage 1) and Table 5 (Stage 2).

7.7 Concomitant Medications

All concomitant medications will be recorded from the time the patient signs the ICF through the End of Treatment Visit and telephone call follow-up. Nonprescription medications, medications given as part of any surgical procedure, and dietary supplements will be included, as will the specific dose/schedule of any systemic corticosteroid agents. The concomitant medication documentation for sexually active females of childbearing potential and sexually active males should support contraceptive usage, as applicable. Concomitant medications that are allowed or prohibited during the study are described in Sections 4.2 and 4.3.

If a severe allergic reaction occurs and is believed to be related to investigational therapy, the Investigator should discontinue treatment (if ongoing) and follow the medically acceptable standard of care. The reaction will be recorded as an AE, and all medications given will be recorded as concomitant medications.

7.8 MRI or CT Scans

Whichever scan modality is used to qualify a patient for enrollment during Screening must be used for the remainder of the study. Imaging assessments are to be performed approximately every 8 weeks during

participation in the study. Imaging evaluation (MRI or CT) may be performed either on the day of a treatment visit, or during the 7 days prior to a treatment visit (during the 5 days prior for the Week 8 evaluation); it should be noted that if an assessment is performed during the days prior to a treatment visit, the results should nonetheless be considered as part of the visit for the week at which the treatment is subsequently administered; for example an MRI performed 3 days prior to the Week 8 visit is technically conducted during the 7th week of study participation, but should be recorded as the "Week 8" imaging assessment. For patients with evidence of disease control ongoing beyond 50 weeks, MRI or CT scans after Week 50 may be performed every 12 weeks (± 14 days).

7.9 Immunological Monitoring Response Assessment

Immune response assessment testing will be performed by a central laboratory. Specific instructions on the collection, processing, and shipment of blood samples are provided in the laboratory manual. The blood samples will be analyzed using a qualified method by the following laboratory:

ABL, Inc.
9800 Medical Center Drive
Building D
Rockville, MD, 20850

7.10 Tumor Tissue Sample Submission

As indicated in the inclusion criteria, submission of a tumor tissue sample is required, whenever available, for study participation. Preferably a paraffin block or 10-12 unstained slides will be submitted prior to study entry. Specific instructions on the collection and shipment of tissue samples will be provided in the laboratory manual.

If tumor tissue is collected and available following initiation of study therapy, or at any time point throughout the duration of the study, then a sample must be submitted for immunohistochemical analysis.

This tumor tissue may be used to evaluate relevant antigen expression (including GAA expression status and infiltration of GAA-specific T-cells), other immune markers and potential additional prognostic factors. Tumor tissue paraffin blocks or unstained slides are preferred.

8. REPORTING ADVERSE EVENTS

8.1 Definitions

The Investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study drug or their clinical significance.

An AE is defined as any untoward medical occurrence in a patient enrolled into this study regardless of its causal relationship to study drug. Patients or their legally authorized representatives will be instructed to contact the Investigator or subinvestigator at any time after signing the informed consent if any symptoms develop. PD and disease-related death will not be considered AEs or SAEs.

A TEAE is defined as any event not present before exposure to study drug or any event already present that worsens in either intensity or frequency after exposure to study drug.

An SAE is defined as any event that

- Results in death,
- Is immediately life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient 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, convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. Please consult Section 8.6 for details regarding the specific mechanism by which SAEs are to be reported.

8.2 Eliciting Adverse Event Information

All AEs that occur from the time the patient or authorized representative signs the ICF through 30 days after the last dose of study drug must be reported in detail on the appropriate eCRF and followed for 30 days after the subject's last dose, or until resolution, whichever comes first. Pre-existing AEs that worsen should be followed until 30 days after the subject's last dose or resolution to the AE level present at study entry. The description of the AE will include the onset date, duration, date of resolution, severity, seriousness (see Section 8.6), etiology, and the likelihood of relationship of the AE to study drug.

At every study visit, patients will be asked nondirective questions to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and over-the-counter medications).

In addition to patient observations, AEs will be documented from any data collected on the eCRF or other documents that are relevant to patient safety. Any allergic reaction to the agents administered as study drug treatment must be reported as an AE.

8.3 Adverse Event Reporting

All AEs reported or observed during the study will be recorded on the AE eCRF. Disease progression in the medical opinion of the physician and/or disease-related morbidity and mortality as a study endpoint will not be considered an AE or SAE. Information to be collected includes drug treatment, dosage, type of event, time of onset, Investigator-specified assessment of severity and relationship to study drug, time of resolution of the event, seriousness, any required treatment or evaluations, and outcome. Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed for 30 days after the subject's last dose, or until resolution, whichever comes first. The MedDRA will be used to code all AEs.

Preexisting conditions (present before the start of the AE collection period) are considered concurrent medical conditions and should not be recorded as AEs. However, if the patient experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded as an AE. Pre-existing AEs that worsen should be followed until 30 days after the subject's last dose or resolution to the AE level present at study entry. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of [condition]").

Insufficient clinical response, efficacy, or pharmacological action should NOT be recorded as an AE. The Investigator must make the distinction between exacerbation of preexisting illness and lack of therapeutic efficacy. Progressive disease is NOT an AE; however some sequelae of PD (ie, pain, neurologic impairment) may be reported as AEs (generally not related to investigational therapy).

Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, require therapy or further diagnosis beyond repeat testing for confirmation, or (if not associated with clinical signs or symptoms) they remain at levels consistent with severe abnormalities despite appropriate medical intervention.

It is requested that when reporting AEs for which potentially redundant CTCAE terms exist, the Investigator utilizes the more clinically-oriented terminology (for example, "anemia" is preferable to "hemoglobin decreased").

It is also requested that in the setting of an allergic reaction or suspected allergic reaction considered by the Investigator to be related to investigational therapy, that the Investigator reports both the specific symptoms associated with the reaction (ie, "urticaria", "dyspnea") and also report the appropriate term indicating the allergic reaction ("allergic reaction" or "anaphylaxis" if appropriate [Immune System Disorders; CTCAE v4.03, page 26]).

8.4 Assessment of Causality

The Investigator's assessment of an AE's relationship to study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

In this study, the investigational medicinal product is SL-701. The relationship of an AE to the investigational product should be classified using the following guidelines:

Related: A temporal relationship exists between the event onset and administration of SL-701. It cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies. In case of cessation or reduction of the dose, the event abates or resolves and reappears upon rechallenge. This includes events that are considered possibly, probably, or definitely related to SL-701.

Not Related: Evidence exists that the AE has an etiology other than the study drug (eg, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication). This includes events that are considered probably not or not related to SL-701. It should be emphasized that ineffective study drug treatment should not be considered as causally related in the context of adverse event reporting (in other words, PD is not considered an AE; however some sequelae of PD may be reported as AEs and should generally be reported as AEs not related to investigational therapy).

The additional medications evaluated in this study are GM-CSF and topical imiquimod (Stage 1) or poly-ICLC (Stage 2) as vaccine adjuvants and bevacizumab as an anti-tumor agent (Stage 2). The relationship of an AE to each of these agents should be classified according to the same guidelines as detailed above.

8.5 Assessment of Severity

The severity of AEs will be assessed using the NCI CTCAE, Version 4.03 (or higher). The intensity of the AE will be rated as mild, moderate, or severe using the following criteria:

Mild: These events require minimal or no treatment and do not interfere with the patient's daily activities. These are generally considered Grade 1 events in the NCI CTCAE.

Moderate: These events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning. These are generally considered Grade 2 events in the NCI CTCAE.

Severe: These events interrupt a patient's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating. These are generally considered Grade 3-4 events in the NCI CTCAE (Grade 4 is generally for AEs that are considered life-threatening).

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent require documentation of onset and duration of each episode.

8.6 Serious Adverse Event Reporting

Any AE considered serious by the Investigator or subinvestigator or that meets the seriousness criteria (Section 8.1) that occurs from signing the ICF through 30 days after last study drug dose must be reported to INC Research within 24 h from the time study site personnel first learn about the event. The SAE report will be completed and faxed to the INC Research Pharmacovigilance Department. However, the Investigator and staff are encouraged to contact the Medical Monitor and the INC Research Pharmacovigilance Department staff at the SAE Hotline number at any time. The SAE Hotline telephone number and fax number are found in the study manual. PD and disease-related death will not be considered AEs or SAEs.

If the patient is hospitalized because of or during the course of an SAE, then a copy of the hospital discharge summary should be faxed to INC Research at the SAE Fax line as soon as it becomes available. Withdrawal from the study and all therapeutic measures will be performed at the discretion of the Investigator or subinvestigator.

The Sponsor will notify appropriate regulatory authorities by telephone or fax transmission of any unexpected, fatal, or life-threatening experience that is determined to be related to the use of the study drug (expedited report) as soon as possible but no later than 7 calendar days after the initial receipt of the information. Initial notification will be followed by a written report within 15 calendar days. For unexpected events associated with the use of the study drug, the Sponsor will notify the regulatory authorities as soon as possible, but no later than 15 days of the initial receipt of information. The Investigator or subinvestigator is responsible for informing the Institutional Review Board (IRB)/Independent Ethics Committee (IEC). Copies of SAE correspondence with all Investigators or subinvestigators, governing authorities, ethics committees, and the Sponsor must be submitted to INC Research for filing.

A patient experiencing 1 or more SAEs will receive treatment and follow-up evaluations by the Investigator or subinvestigator or will be referred to another appropriate physician for treatment and follow-up. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

Study endpoints in GBM patients include disease-related mortality and morbidity which will not be reported as expedited IND safety reports, unless there is a serious and unexpected event with evidence of a causal relationship between study drug and the event. As appropriate and based on the frequency of occurrence, SAEs in the study will be reported to FDA at an appropriate interval, such as inclusion in the periodic update IND annual report.

The following SAEs will not be reported individually in an expedited manner because they are anticipated to occur in the GBM study population receiving stand of care treatment at some frequency independent of study drug exposure:

- Progression of disease, glioma.
- Death as a consequence of the underlying disease, glioma.

Please consult Section 8.1 regarding a comprehensive definition of SAEs.

8.7 Pregnancy

Women with known or suspected pregnancy are excluded from the study. However, if pregnancy is discovered after administration of study drug, the Investigator must report information using the Pregnancy Report Form to the INC Research Pharmacovigilance Department staff at the SAE Hotline number at any time. The SAE Hotline telephone number and fax number are found in the study manual.

All pregnancies will be followed up to final outcome, using the pregnancy follow-up form. The outcome, including any premature termination, must be reported to the INC Research Pharmacovigilance Department staff. The pregnancy is not considered an AE; however pregnancy complications, including miscarriage or spontaneous abortion, are considered AEs. Any untoward outcome for the mother or infant is considered an SAE.

8.8 Criteria for Stopping Study

The occurrence of any medically important AE that could impact the safety of other patients may prompt a review of the available safety data and may lead to the discontinuation of the study after discussions between the Medical Monitor and the Sponsor.

9. STATISTICAL METHODS

A complete description of the statistical analyses and methods will be available in a Statistical Analysis Plan that will be finalized before the database is locked.

Descriptive statistics used to summarize continuous variables will include the number of non-missing observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using the number of and percentage of patients. Missing data will not be imputed. All data obtained in this study will be analyzed using SAS® software (version 9.3 or higher).

9.1 Stage 1 Sample Size

The initially planned sample size of 100 patients was based on the following assumptions for the 2 alternative primary endpoints of OS-12 and ORR (Wick 2010, van den Brent 2009, and Batchelor 2013):

OS-12:

- The null hypothesis is that OS-12 for patients treated with SL-701 is ≤25%;
- The alternative hypothesis is that OS-12 for patients treated with SL-701 is ≥40%;
- Testing will be by an exact one-sample binomial superiority test with a type I error rate of 1.25%, one-sided (ie, a Bonferroni correction will be applied to the usual type I error rate of 2.5% to adjust for the analysis of 2 primary endpoints).

ORR (by modified RANO criteria):

- The null hypothesis is that ORR for patients treated with SL-701 is ≤10%;
- The alternative hypothesis is that ORR for patients treated with SL-701 is ≥25%;
- Testing will be by an exact one-sample binomial superiority test with type I error rate of 1.25%, one-sided;
- At least 80 patients will be evaluable for ORR.

Based on these assumptions, the power for the initially planned sample size was approximately 82% for OS-12 and 92% for ORR. Accrual to Stage 1 one of the study was discontinued following the accrual of 46 patients (all evaluable for ORR) who received SL-701 emulsion, GM-CSF, and imiquimod. Consequently the power for Stage 1 given the actual enrollment was approximately 48% for OS-12 and 62% for ORR.

9.2 Stage 2 Sample Size

A total of 30 patients are planned to be enrolled in Stage 2. In this stage, the null and alternative hypotheses for OS-12 will remain the same as those utilized in Stage 1, described in Section 9.1. The null and alternative hypotheses for ORR will be ≤40% and ≥60%, respectively. Testing in Stage 2 will be at a type I error rate of 5%, one-sided. If 30 patients (assumed all evaluable for ORR) are enrolled in Stage 2, the power is approximately 71% for OS-12 and 55% for ORR.

9.3 Analysis Populations

Full Analysis Set

The full analysis set (FAS) will include all enrolled patients who received at least 1 dose of study drug. The FAS will be used to analyze all safety data and any efficacy assessments based solely on survival (ie, OS-12 and OS).

Objective Response Evaluable Set

The objective response evaluable (ORE) set will consist of all patients in the full analysis set who had measurable tumors on MRI scans at Screening. The ORE set will be used to analyze any efficacy

assessments that involve objective response (ie, ORR, PFS-6, PFS, and DR).

9.4 Patient Disposition

The number of patients who were screened, entered and completed the study, as well as the reason for discontinuing study drug or withdrawing from the study will be tabulated. The reason for discontinuing study drug or withdrawing from the study will be listed by patient.

9.5 Demographics and Baseline Data

Demographic (eg, gender, age, race, ethnicity) and baseline characteristics (eg, KPS, height, weight, and prior therapy) will be summarized using descriptive statistics. Supportive data will be listed by patient.

Medical history will be summarized for the FAS using the number of observations and percentage of patients reporting each category.

9.6 Study Drug Administration

The number of doses of study drug administered to each patient will be summarized using descriptive statistics. In Stage 1, information collected in the paper diary (imiquimod diary) will be used to document patient compliance with the imiquimod cream self-application 24 h after the SL-701 emulsion injection.

9.7 Analysis of Efficacy Endpoints

9.7.1 Primary Endpoints

Exact one-sample binomial tests with a type I error rate of 1.25%, one-sided for Stage 1 of the study and 5%, one-sided for Stage 2 of the study will assess whether the percentage of patients surviving 12 months after initiation of SL-701 (ie, OS-12) is >25%. Exact 2-sided 97.5% (Stage 1) or 90% (Stage 2) confidence intervals (CIs) will also be reported for OS-12. The analysis of this primary endpoint will be conducted using the FAS. (An additional, secondary evaluation of OS-12 per Kaplan-Meier estimate will also be conducted with non-exact CIs).

Exact one-sample binomial tests with a type I error rate of 1.25%, one-sided for Stage 1 and 5%, one-sided for Stage 2 will assess whether the percentage of patients who have a best response of either CR or PR documented on 2 consecutive MRIs obtained ≥4 weeks apart (ie, ORR) is >10%. Exact 2-sided 97.5% (Stage 1) or 90% (Stage 2) CIs will also be reported for ORR. The analysis of this primary endpoint will be conducted using the ORE set and the modified RANO criteria.

The clinical study will be considered to have met its efficacy objectives if either one of the primary endpoints achieves statistical significance.

9.7.2 Secondary Endpoints

The following analyses will be performed for the Stage 1 and Stage 2 cohorts.

Descriptive statistics will be used to summarize all secondary efficacy endpoints; no inferential testing will be performed. Two-sided 95% CIs will be reported for key descriptive statistics as noted below.

Median values for the DR, PFS, and OS (in months) and their 2-sided 95% (Stage 1) or 90% (Stage 2) CIs will be estimated using the method of Kaplan-Meier. The analysis of OR and PFS will use the modified RANO criteria and the ORE set. The analysis of OS will use the FAS.

In a sensitivity analysis, values of ORR, DR, and PFS will be estimated as judged by RECIST (version 1.1). An exact 2-sided 97.5% (Stage 1) or 90% (Stage 2) CI will be reported for ORR. Median values for DR and PFS (in months) and their 2-sided 95% CIs will be estimated using the method of Kaplan-Meier. Analyses of ORR, DR, and PFS using RECIST (version 1.1) will use the ORE set.

The distributions of DR and PFS will be displayed by plotting the survival distribution function estimated using the Kaplan-Meier methodology as a function of time. These distributions will be shown using both the modified RANO criteria and RECIST (version 1.1) using the ORE set. PFS-6 will be evaluated both by direct proportion and via Kaplan-Meier estimate.

The magnitude of immune response in PBMCs will be summarized by study visit. Spot counts for glioma-associated antigen (ELISPOT) will be summarized descriptively by study visit using the geometric mean and coefficient of variation. Similarly, the number of GAA-specific T-cells infiltrating post-vaccine tumor tissue will be summarized descriptively by study visit using the geometric mean and coefficient of variation.

The percentage of surviving patients who have been considered to have mounted an immune response to each of the antigens will be reported by study visit along with its exact 2-sided 95% (Stage 1) or 90% (Stage 2) CI.

9.7.3 Exploratory Endpoints

Cox regression will be used to determine whether there is a correlation between various measures of tumor efficacy (ie, PFS and OS) and measures of immunogenicity. Cox regression will also be used to determine whether there is an association between PFS or OS and the presence of GAA in or infiltration of GAA-specific T-cells into post-vaccine tumor tissue. These analyses will be conducted using the ORE set for PFS and the FAS for OS.

9.8 Safety Analysis

The FAS will be used to report all safety analyses.

9.8.1 Adverse Events

An AE will be considered treatment-emergent (ie, a TEAE) if it starts on or after the time of the first dose of study drug and up to 30 days after the last dose of study drug. AEs will be summarized by MedDRA™, Version 13.1 (or higher), system organ class (SOC) and PT. The severity of AEs will also be summarized by NCI CTCAE, Version 4.03 (or higher). Non-TEAEs will be included in the patient listings and flagged as such but will not be included in the summary tables. Where an AE date is partial or missing, and it is unclear whether the AE is treatment-emergent, the AE will be assumed to be treatment-emergent.

The number and percentage of patients who experience TEAEs will be summarized overall by SOC and PT and will also be summarized based on severity and causality.

Descriptive analysis of AEs will include incidence of TEAEs and SAEs grouped by:

- SOC and PT.
- SOC, PT and severity.

- SOC, PT and causality.
- SOC and PT leading to discontinuation from the study.
- SOC and PT for events with CTCAE ≥Grade 3.
- SOC and PT leading to death.

Individual listings of all AEs will also be provided.

9.8.2 Laboratory Parameters

Laboratory results (hematology, serum chemistry, coagulation parameters, and urinalysis) will be classified according to NCI CTCAE, Version 4.03 (or higher). Laboratory results not corresponding to an NCI CTCAE term will not be graded. Incidences of laboratory abnormalities will be summarized with descriptive statistics by study visit.

Shift tables will display intra-individual changes from baseline to each study visit using categorizations provided by the local laboratory. Categorization will be done by converting the local laboratory specific normal ranges into missing, low, normal, and high. Shift tables will also be shown for intra-individual changes from baseline in CTCAE grade for each study visit. CTCAE <Grade 3 at baseline will be combined into a single category for the shift table.

Laboratory data will be listed and abnormal results will be flagged.

9.8.3 Vital Signs

Vital signs will be summarized by study visit using descriptive statistics.

9.8.4 Physical Examination

The analysis of physical examination will focus on patients who develop abnormalities post-baseline or whose evaluations worsen after baseline. Frequency tables will display the number and frequency of patients with any abnormalities by study visit. The results of abnormal physical examinations will also be listed.

9.9 Interim Analysis

There is no interim efficacy analysis planned for this study.

9.10 Study Completion, Extension Phase, End-of-Study

The study is considered complete when sufficient information is available to enable assessment of the primary endpoint(s) and other critical secondary endpoints. In the weeks subsequent to a determination that sufficient information is available for these assessments, a date for database lock will be assigned, and any outstanding inquiries concerning data elements will be resolved. The **Study Completion** date will be the date beyond which study data is no longer entered into the primary database (this study completion date generally precedes the date on which the database lock occurs by several weeks/months).

In the event that patients continue to receive investigational therapy without evidence of PD or intolerable toxicity at the time of study completion, and the Investigator(s) believe that ongoing administration of investigational therapy is likely to confer additional benefit, a **Study Extension Phase** may be implemented, in which investigational therapy is made available to patients who continue to meet criteria

for therapy (and who provide an additional informed consent in order to receive ongoing therapy). During the **Study Extension Phase**, Investigators are encouraged to continue evaluation of patients (including laboratory and imaging assessments) at a schedule similar to that which was stipulated during the conduct of the study. Data collection by the Sponsor during this Extension Phase will be limited to information pertaining to study drug administration (dose, chronology), AEs, SAEs, and reasons for discontinuation of study therapy (supplemental efficacy data including information on patients' overall survival status may be considered if applicable). The **End-of-Study** occurs approximately 30 days after the last patient has discontinued study therapy.

10. PATIENT DATA HANDLING AND QUALITY ASSURANCE

10.1 Case Report Forms

As part of the responsibilities assumed by participating in the study, the Investigator or subinvestigator agrees to maintain adequate case histories for the patients enrolled as part of the research under this protocol. The Investigator or subinvestigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents include laboratory reports and MRI or CT scans.

An eCRF will be used. All eCRF information is to be completed. If an item is not available or is not applicable, this fact should be indicated. Blank fields should not be present unless otherwise directed. Each completed eCRF must be reviewed, signed, and dated by the Investigator or subinvestigator in a timely manner.

10.2 Monitoring of the Study

The clinical monitor, as a representative of the Sponsor, has the obligation to follow the study closely. In doing so, the monitor will visit the Investigator or subinvestigator, other study staff, and the study facility at periodic intervals, in addition to maintaining necessary contact through telephone, e-mail, and letter correspondence. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigator or subinvestigator and staff. The monitor will assure that the hospital or outpatient facility pharmacy staff maintains appropriate study drug accountability and dose-preparation records. The monitor will also ensure that the study drugs are stored under appropriate conditions.

All aspects of the study will be carefully monitored by the Sponsor or its designee for compliance with applicable government regulation with respect to current International Conference on Harmonization (ICH) E6(R1) guideline, Good Clinical Practice: Consolidated Guideline, and current standard operating procedures.

10.3 Inspection of Records

The Investigator or subinvestigator and institution involved in the study will permit study-related monitoring, audits, IRB/ IEC review, and regulatory inspection(s) by providing direct access to all study records. In the event of an audit, the Investigator or subinvestigator agrees to allow the Sponsor, representatives of the Sponsor, the FDA, or other regulatory agency access to all study records.

The Investigator or subinvestigator should promptly notify the Sponsor and the CRO of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the Sponsor.

10.4 Study Record Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator or subinvestigator or institution as to when these documents no longer need to be retained.

11. ADMINISTRATIVE CONSIDERATIONS

The following administrative items are meant to guide the Investigator or subinvestigator in the conduct of the study but may be subject to change based on industry and government standard operating procedures or working practice documents or guidelines. Administrative change will be reported to the IRB/IEC but will not result in protocol amendments.

11.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient (or the patient's legal representative), except as necessary for monitoring and auditing by the Sponsor, its designee, the FDA, the European Medicines Agency (EMA), or the IRB/IEC.

The Investigator or subinvestigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

11.2 Institutional Review Board/Research Ethics Board

Federal regulations and the ICH guidelines require that approval be obtained from an IRB/IEC before participation of human patients in research studies. Before the study onset, the protocol, informed consent, advertisements to be used for patient recruitment, and any other written information regarding this study to be provided to the patient or the patient's legal representative must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH E6 (R1) guidelines will be maintained by the study site and will be available for review by the Sponsor or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title and/or protocol number, and the date approval and/or favorable opinion was granted.

The Investigator or subinvestigator is responsible for obtaining continued review of the clinical research at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The Investigator or subinvestigator must supply the Sponsor or its designee with written documentation of continued review of the clinical research.

11.3 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the patient, must be reviewed and approved by the Sponsor or its designee. Amendments to the protocol must be submitted in writing to the Investigator's or subinvestigator's IRB/IEC and, if applicable, to the appropriate regulatory authorities for approval before patients can be enrolled into an amended protocol.

11.4 Informed Consent

Written informed consent, in compliance with US Title 21 Code of Federal Regulations (CFR), Part 50, current ICH E6 (E1) guidelines, and other applicable regulatory requirements, shall be obtained from each patient or legally authorized representative before entering the study or performing any unusual or nonroutine procedure that involves risk to the patient. An ICF template may be provided by the Sponsor to study sites. If any institution-specific modifications to study-related procedures are proposed or made by the study site, the consent should be reviewed by the Sponsor and/or its designee, if appropriate, before IRB/IEC submission. Once reviewed, the ICF will be submitted by the Investigator or subinvestigator to his or her IRB/IEC for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating patients or their legally authorized representatives must sign the revised ICF.

Before recruitment and enrollment, each prospective patient or his/her legally authorized representative will be given a full explanation of the study and allowed to read the approved ICF. Once the Investigator or subinvestigator is assured that the patient/legal representative understands the implications of participating in the study, the patient/legal representative will be asked to give consent to participate in the study by signing the ICF.

The Investigator or subinvestigator shall provide a copy of the signed informed consent to the patient and/or legal representative. The original form shall be maintained in the patient's medical records at the study site.

11.5 Protocol Violations and Deviations

The Investigator or subinvestigator or designee must document and explain in the patient's source documentation any deviation from the approved protocol. The Investigator or subinvestigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study patients without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendment(s) should be submitted to the IRB/IEC for review and approval, to the Sponsor for agreement, and to the regulatory authorities, if required.

A deviation from the protocol is an unintended and/or unanticipated departure from the procedures and/or processes approved by the Sponsor and the IRB/IEC and agreed to by the Investigator or subinvestigator. Deviations usually have an impact on individual patients or a small group of patients and do not involve inclusion/exclusion or primary endpoint criteria. A protocol violation occurs when there is nonadherence

to the protocol that results in a significant, additional risk to the patient, when the patient or Investigator or subinvestigator has failed to adhere to significant protocol requirements (eg, inclusion/exclusion criteria) and the patient was enrolled without prior Sponsor approval, or when there is nonadherence to FDA or other applicable regulations and/or ICH E6 (R1) guidelines.

The clinical monitor will document protocol violations and deviations throughout the course of monitoring visits. The monitor will notify the Investigator or subinvestigator during a visit and/or in writing of all violations and deviations. The IRB/IEC should be notified of all protocol violations and deviations in a timely manner.

11.6 Study Reporting Requirements

By participating in this study, the Investigator or subinvestigator agrees to submit reports of SAEs according to the timeline and method outlined in the protocol. In addition, the Investigator or subinvestigator agrees to submit annual reports to his/her IRB/IEC as appropriate. The Investigator or subinvestigator also agrees to provide the Sponsor with an adequate report shortly after completion of the Investigator's or subinvestigator's participation in the study.

11.7 Financial Disclosure and Obligations

The Investigators and subinvestigators are required to provide financial disclosure information to allow the Sponsor to submit the complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the Investigator and subinvestigators must provide to the Sponsor a commitment to update promptly this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.

Neither the Sponsor nor the CRO is financially responsible for further testing/treatment of any medical condition, which may be detected during the screening process. In addition, in the absence of specific arrangements, neither the Sponsor nor the CRO is financially responsible for further treatment of the patient's disease.

11.8 Investigator Documentation

Before beginning the study, the Investigator will be asked to comply with ICH E6 (R1) 8.2, 21 CFR, and other applicable regulations by providing the following essential documents, including but not limited to:

- An original Investigator-signed Investigator Agreement page of the protocol.
- An IRB/IEC-approved ICF, samples of study site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the patient or legal representative.
- IRB/IEC approval.
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572.
- Curriculum vitae for the Investigator and each subinvestigator listed on Form FDA 1572. Current licensure must be noted on the curriculum vitae. They will be signed and dated by the Investigator and subinvestigators at study start-up, indicating that they are accurate and current.

- Financial disclosure information to allow the Sponsor to submit complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the Investigator must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.
- Laboratory certifications and reference ranges for any local laboratories used by the study site, in accordance with 42 CFR 493.

11.9 Study Conduct

The Investigator agrees that the study will be conducted according to the principles of the ICH E6 (R1) and the principles of the World Medical Association Declaration of Helsinki. The Investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations.

11.10 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the Sponsor will be responsible for these activities and will work with the Investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The Sponsor has final approval authority over all such issues.

Data are the property of the Sponsor and cannot be published without prior authorization from the Sponsor, but data and publication thereof will not be unduly withheld.

12. INVESTIGATOR'S STATEMENT

I agree to conduct the study as described in the protocol entitled "A Phase 1/2 Study of SL-701, a Subcutaneously Injected Multivalent Glioma-Associated Antigen Vaccine, in Adult Patients with Recurrent Glioblastoma Multiforme" in accordance with Good Clinical Practice guidelines, the Declaration of Helsinki, and all applicable law and regulations. I have read and understand all sections of the protocol, including Section 11, Administrative Considerations.

Principal Investigator's Signature Date

Principal Investigator's Name (printed)

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Package Insert References for GM-CSF and Imiquimod:

GM-CSF United States Package Insert.
http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=723782d7-a2ab-4cc6-a767-387975ccec80

Imiquimod. United States Package Insert.
http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=7fccca4e-fb8f-42b8-9555-8f78a5804ed3

14. APPENDICES

14.1 Karnofsky Performance Scale

From: Oxford Textbook of Palliative Medicine, Oxford University Press. 1993; 109

100	Normal, no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death is not imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

14.2 RANO Criteria for Response Assessment

From: Wen 2010.

Response	Criteria
Complete Response	Requires all of the following: complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; stable or improved nonenhancing (T2FLAIR) lesions; patients must be off corticosteroids (or on physiologic replacement doses only); and stable or improved clinically. Note: Patients with nonmeasurable disease only cannot have a complete response; the best response possible is stable disease.
Partial Response	Requires all of the following:≥ 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks; no progression of nonmeasurable disease; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan; the corticosteroid dose at the time of the scan evaluation should be no greater that the dose at the time of baseline scan; and stable or improved clinically. Note: Patients with nonmeasurable disease only cannot have a partial response; the best response possible is stable disease.
Stable Disease	Requires all of the following: does not qualify for complete response, partial response, or progression; stable nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging show that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.
Progressive Disease	Defined by any of the following: ≥ 25% increase in the sum of the products of maximal perpendicular diameters of enhancing tumor(s) compared to the smaller of pre-SL-701 baseline or best response following initiation of SL-701; New measureable contrast-enhancing lesion(s) defined as lesion(s) that measure at least 1 cm in at least 2 planes; Significant clinical decline not attributable to co-morbid event or change in concurrently administered medication.
NOTE: All measurable and nonmeasurable lesions must be assessed using the same techniques as at baseline. Abbreviation: FLAIR, fluid-attenuated inversion recovery.	

14.3 RECIST Criteria (version 1.1) for Response Evaluation

From: Eisenhauer 2009.

Evaluation of target lesions	
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Evaluation of non-target lesions	
Complete Response (CR)	Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10mm short axis).
Non-CR/Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.
Progressive Disease (PD)	Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).