A Phase I Trial of IRS-1 HSV C134 (IND 17296) Administered Intratumorally in Patients with Recurrent Malignant Glioma

Study Protocol & Statistical Analysis Plan

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STUDY SYNOPSIS

Objective:	To obtain safety information in small cohorts of individuals, with cohorts to receive escalating doses of IRS-1 HSV C134 (hereafter C134). Safety will be assessed at each dose level before proceeding to the next dose. Biologic secondary objectives include characterization of the *in situ* activity of C134 after intratumoral inoculation and of the local and systemic immune responses to C134. As a clinical secondary objective, patients will be followed serially by MRI for potential clinical response to C134. The clinical strategy takes advantage of the virus' ability to infect and lyse tumor cells and the potential for enhancement of this effect by the induction of an anti-tumor immune response.
Treatment Indication:	Progressive growth of *glioblastoma multiforme*, anaplastic astrocytoma or gliosarcoma after radiation therapy.
Clinical Phase:	Phase 1 (open-label)
Design:	Single dose of C134 infused through catheters into region(s) of tumor defined by MRI. Dosage escalation proceeds only after a minimum of 24 days of observation, if incidence of Grade III/IV toxicities is acceptable. Dose increases or reductions will be determined using a modified Continual Reassessment Method (CRM); extent of dose changes for subsequent subjects will be increased up to, but not exceeding the next higher dose level (1 log). Dose modifications will utilize a modified CRM for each successive subject until an MTD or the maximal planned dose is reached.
Study Duration Per Patient:	12 months
Subject Population:	4 to 24 patients with recurrent/progressive *glioblastoma multiforme*, anaplastic astrocytoma or gliosarcoma depending on toxicities.
Study Medication and Dosage:	Dose escalations of up to, but not exceeding the next highest dose level (1 log). Dose escalations from 1×10^6 to 1×10^8 plaque-forming units of C134.
Safety Evaluations:	Follow-up evaluations using routine laboratory analyses and clinical measurements of neurological function and evidence of C134-related toxicity. Studies to evaluate the possibility of C134 shedding will also be conducted. Patients will be observed closely during the planned post-treatment hospitalization period, followed by outpatient evaluations done at Day 10 and Day 28, then months 3, 6, and 12, subject to disease progression.
Study Endpoints	Primary: CRM-estimated highest safe dose or maximally planned dose if no dose-limiting toxicity observed. Secondary: Time to progression, survival, biologic assessments.

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Clinical Protocol: A Phase I Trial of IRS-1 HSV C134 Administered Intratumorally in Patients with Recurrent Malignant Glioma

1. OBJECTIVES

Lay Abstract: C134 is a next-generation oncolytic herpes simplex virus (oHSV) that is conditionally replication competent; that is, similar to G207, a first generation oHSV, it can replicate in tumor cells, but not in normal cells, thus killing the tumor cells directly through this process. Replication of C134 in the tumor itself not only kills the infected tumor cells, but causes the tumor cell to act as a factory to produce new virus. These virus particles are released as the tumor cell dies, and can then proceed to infect other tumor cells in the vicinity, and continue the process of tumor kill. In addition to this direct oncolytic activity, the virus promotes an immune response against surviving tumor cells, which increases the antitumor effect of the therapy. The virus expresses a gene from another virus from the same overall virus family, human cytomegalovirus, that allows it to replicate better in the tumor cells than G207. However, the virus has also been genetically engineered to minimize the production of any toxic effects for the patient receiving the therapy.

1.1 Primary Objective

To determine the safety and tolerability of stereotactic intracerebral injections of escalating doses of C134 virus, and to determine the maximally tolerated dose (MTD) of C134.

1.2 Secondary Objectives

To obtain preliminary information about the potential benefit of C134 in the treatment of patients with recurrent malignant gliomas including relevant data on markers of efficacy, including time to tumor progression and patient survival.

2. BACKGROUND

2.1 Glioblastoma multiforme.

Malignant gliomas are the most frequently occurring primary brain tumors (1). *Glioblastoma multiforme*, the most malignant of these neoplasms, has also proven to be one of the most fatal and refractory cancers (2, 3). Median time to progression and median survival have not changed in the past fifty years for these tumors and have thus engendered intensive exploration into the study of additional treatment modalities (4).

2.2 Experimental therapies and conditionally replication competent viruses

Current molecular therapies for malignant glioma fall into three major groups amongst which there is considerable overlap: ligand-based therapies, immunotherapies, and vector-mediated therapies (5). While several different modified viruses are under investigation for the treatment of human malignancies, this application focuses on conditionally replication competent, $\Delta\gamma_1$34.5 HSV.

Oncolytic HSV-1 therapy. Herpes simplex viruses are large, enveloped, DNA viruses with an approximately 152 kilobase (kb) pair genome. Genetically modified HSV are attractive as replication-competent, oncolytic vectors for a number of reasons: 1) procedures for constructing novel HSV are well established; 2) multiple genes can be deleted and/or replaced with therapeutic foreign genes without affecting the replication capacity of the virus; 3) considerable experience with the biology of HSV and its behavior in humans and nonhuman primates exists; and 4) modified herpesviruses retain sensitivity to standard antiviral drug therapy as a “built-in” safety feature (5-7).

Genes producing neurovirulence of HSV-1 are distinct from those that confer oncolytic properties. Deletion of the HSV-1 neurovirulence gene allows the safe administration of these oncolytic vectors to

mitotically active CNS tumors. Though capable of entry into non-dividing normal cells in the CNS, these $\Delta\gamma_1$34.5 HSV cannot replicate efficiently except in actively dividing cells such as tumor cells (8-10), and hence are referred to as tumor-selective viruses. HSV-1 mutants with deletions of both copies of the $\gamma_1$34.5 gene have shown significant efficacy for therapy of brain malignancies in preclinical animal models, and have been demonstrated to be safe in Phase I and II trials in both the United States and Great Britain (7, 11, 12). The virus examined in the U.S. trial, G207, contains an additional mutation in the viral ribonucleotide reductase gene, U_L39, as an additional safety feature to limit viral growth (1).

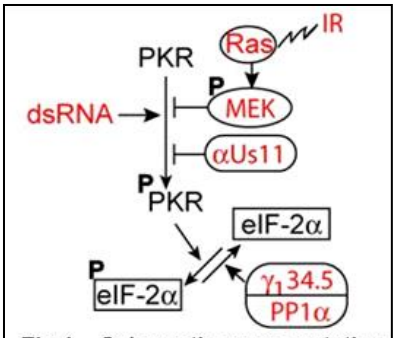


Fig 1 – Schematic representation of the PKR eIF-2α pathway
Included are activators (dsRNA) and inhibitors of PKR activation (MEK and αUs11) as well as the $\gamma_1$34.5 protein phosphatase 1α (PP1a) complex that dephosphorylates eIF-2α.

2.3 Innate antiviral response pathway and viral countermeasures.

Eukaryotic cells contain an innate defense system that targets viral infection (13). A principal component of this system is protein kinase R (PKR), which limits viral gene expression and replication in human cells (**Figure 1**) (14). Low levels of this evolutionarily conserved, interferon-inducible kinase are present in a non-active form in unstressed cells. However, its producti on is induced by type I interferons or double-stranded RNA (dsRNA) produced during viral infection (13). Upon binding dsRNA, the kinase activates and phosphorylates itself as well as cellular proteins involved in the antiviral response. The best characterized of the substrates is the α subunit of eukaryotic translation initiation factor 2 (eIF-2α) (15, 16). Phosphorylation of eIF-2α prevents recycling of a critical translation initiation factor, thus limiting viral and cellular protein synthesis in the infected cell (14).The PKR-mediated host protein shutoff response, in addition to serving as an antiviral defense system in the cell, is also involved in cellular homeostasis. Consequently, second messenger signaling pathways in the cell and PKR modulate one another's activity in the cell. These pathways can block PKR activation during periods of cellular stress or cellular replication. For example, upregulation of mitogen-activated protein kinase (MAPK) activity in the cell (mediated by a component of this pathway, MEK) blocks PKR activation during growth factor stimulation or following radiation (depicted as "IR" in **Figure 1**) (17, 18). Likewise, activated PKR has also been shown to modulate MAPK function in the cell and is thought to act as a signal integration point between the pathways (19). While regulation of protein synthesis initiation is the best characterized of the PKR antiviral functions, the kinase also modulates other cellular functions, including: bulk protein degradation in the cell (also called autophagy), RNA transcription, and signal transduction in the cell (17, 20-22). Viruses have evolved to selectively regulate the cellular responses to infection by targeting different components of the PKR pathway.

2.4 Viral evasion of PKR.

Efficient viral protein synthesis is essential for viral replication. Consequently, viruses have evolved genes whose products specifically target the PKR protein shutoff response. Those relevant to this proposal are summarized in the next three subsections.

2.4.1. The HSV-1 γ134.5 gene encodes a multifunctional protein that prevents PKR-mediated protein shutoff during infection (9, 23). One function allows late viral protein synthesis in infected cells, and is encoded within the 3' gene domain (8). During infection, wild-type HSV-1 produces complementary mRNA transcripts that anneal, forming stable dsRNA which triggers the dimerization and activation of dsRNA-activated host protein kinase R (PKR). The HSV-1 $\gamma_1$34.5 protein (ICP34.5) overcomes this PKR-mediated host protein shutoff by binding and recruiting a host phosphatase that specifically dephosphorylates eIF-2α, allowing continued viral protein synthesis (hereafter referred to as the HSV wild-type protein synthesis phenotype) in the infected cell (**Figure 1**) (24, 25). Recombinant viruses that lack the $\gamma_1$34.5 gene ($\Delta\gamma_1$34.5 HSV) are incapable of maintaining eIF-2α in an

unphosphorylated form and therefore are unable to maintain protein synthesis in the infected cell (26). Cessation of protein synthesis occurs at the onset of viral DNA synthesis late in infection, essentially eliminating bulk synthesis of viral structural proteins necessary for viral capsid formation (26). Consequently, $\Delta\gamma_1$34.5 HSV replicate inefficiently and produce fewer progeny virions in cells with intact PKR pathways (27).

The $\gamma_1$34.5 gene also encodes a second function, neurovirulence, enabling efficient viral replication in post-mitotic neuronal cells (8-10, 24). Neurovirulence and protein synthesis functions encoded by the $\gamma_1$34.5 gene are discrete and separable. $\Delta\gamma_1$34.5 HSV are incapable of efficient replication after direct inoculation in the CNS and do not produce encephalitis (9). As such, $\Delta\gamma_1$34.5 HSV vectors have been developed as anti-tumor agents for CNS-based malignancies. Whereas 50-100 PFU of wildtype HSV will produce encephalitis and death in half of the mice inoculated intracerebrally, more than 1 x 10^7 PFU are required to produce encephalitis and death with a $\Delta\gamma_1$34.5 HSV recombinant (9).

2.4.2 Cryptic HSV-1 PKR-evasion genes. $\Delta\gamma_1$34.5 HSV can develop secondary mutations following serial infection in cultured cells that result in improved late viral protein synthesis and restore viral evasion of PKR (27, 28). Two mutations have been described. The first mutation results in the earlier expression of an HSV-1 RNA-binding protein, Us11 (αUs11), and prevents PKR activation and dimerization (**Figure 1**) (28-31). Another suppressor mutant has been described that maps outside of the U_S8-12 domain (27). This suppressor mutant does not alter Us11 kinetic expression, is more virulent than the parent virus (LD_{50} of 4.8 x10^5) and its anti-PKR activity appears to be mediated by a different mechanism which involves PKR dephosphorylation (27).

2.4.3 HCMV and PKR evasion. HCMV, like HSV, produces complementary mRNA following infection and is at risk for forming dsRNA and triggering PKR activation. Two genetically related HCMV genes, IRS1 and TRS1, block PKR function in the infected cell (32, 33). The two genes share a common 5' sequence but diverge in the 3' domain. Studies performed by our group and others (32) have shown that the IRS1 and TRS1 genes are both capable of PKR-mediated protein shutoff. Child et al. showed that the HCMV gene could complement a defective vaccinia virus and described a dsRNA binding domain in the N-terminal shared-protein domain (32). Our studies show that the HCMV genes independently complemented $\Delta\gamma_1$34.5 late viral protein synthesis and preliminary data show that the HCMV genes block PKR activation by a different mechanism than wild-type or recombinant HSV. In addition to this shared function with IRS1, the TRS1 gene encodes a unique function. The TRS1 gene is integral to HCMV viral replication in cell culture. In contrast, the IRS1 gene is readily eliminated from the virus without affecting growth in cell culture (34, 35).

2.5 $\Delta\gamma_1$34.5 HSV-based therapy.

Some tumor cells contain mutations that enable $\Delta\gamma_1$34.5 HSV late viral protein synthesis and enhance replication (36-42). In general, these mutations either occur directly in the PKR/ eIF-2α pathway or they indirectly affect PKR function by upregulating MAPK activity (37, 38, 43). In addition to mutations, ionizing radiation (IR) has been shown to upregulate MAPK activity, thereby facilitating late viral protein synthesis and replication of $\Delta\gamma_1$34.5 HSV in gliomas (18, 44). Direct damage to the glioma cell by replicating virus may represent only one component of HSV based anti-glioma effect. Immunologic response to the virus and exposed tumor antigens may also contribute to the mechanism of $\Delta\gamma_1$34.5 HSV-based therapy in gliomas.

A recently published study, and preliminary studies by our group, indicate that the PKR pathway is functionally intact in gliomas susceptible to oncolysis by $\Delta\gamma_1$34.5 HSV (40). Furthermore, our preliminary data indicate that $\Delta\gamma_1$34.5 HSV do not synthesize late viral proteins or replicate efficiently in malignant glioma cell culture monolayers or in *in vivo* tumor studies (**Figure 3A-C** and data not shown). Despite this inefficient replication, oncolytic HSV improve survival in *in vivo* tumor studies. While encouraging, current $\Delta\gamma_1$34.5 vectors are unable to consistently eliminate the entire tumor.

2.6 Strategies to improve HSV antiglioma therapy

The ultimate goal of oncolytic viral therapy is to achieve maximum tumor cell killing while retaining safety in surrounding normal tissue. To achieve this goal, engineered viruses must be able to selectively

replicate and spread throughout the tumor bed without affecting adjacent normal tissue. While the $\Delta\gamma_1$34.5 recombinants are safe for intracranial administration, these first generation vectors are limited in their replication in tumors and ultimately most patients treated with oncolytic HSV have died from their tumor (11). To improve $\Delta\gamma_1$34.5-based therapy, modifications of the virus have focused on improving viral replication, spread within the tumor bed, and enhancing bystander damage to uninfected tumor cells.

2.6.1 Improving Viral Replication.

2.6.1.1 Irradiation. Initial studies showed that intratumor injection of the $\Delta\gamma_1$34.5 into U87-MG tumors in nude mice, followed by irradiation improved survival of mice over either therapy alone (45). Further studies have demonstrated that in multiple tumor models, IR improves the replication of a variety of recombinants, including a virus containing a copy of the $\gamma_1$34.5 gene (46, 47). Maximal effects seemed to occur when IR was administered between 6 and 24 hours after viral dosing, and occurred over a large dose range (5-20 Gy). Improved viral protein synthesis and increased viral replication after external beam ionizing radiation (IR) accounted for at least part of the mechanism of the increased tumor-specific killing (18, 44). Importantly, these results do not appear to be limited to $\Delta\gamma_1$34.5 HSV vectors, and no increased toxicity was noted with this combined treatment.

2.6.1.2 Second site mutations. Serial passage of $\Delta\gamma_1$34.5 HSV in tumor cells in culture selects for mutations which allow for improved late viral protein synthesis, and improved viral replication in the tumor as described in section B.4.2 (28, 31, 48). Initial reports (2001) indicate that the αUS11 compensatory mutant was aneurovirulent (LD_{50}>6 x10^5); however, it was engineered in a more neurovirulent strain of HSV-1 which limited maximal LD_{50} testing. No intracranial tumor studies were ever published with the αUS11 recombinant and it was developed for treatment of prostate tumors (31, 49).

2.6.1.3 Tumor targeting of wild-type HSV-1. Another approach is to selectively target wild-type HSV to tumors by modification of HSV glycoproteins required for virus entry. Recombinant HSV have been constructed that exclusively enter tumor cells through tumor-specific receptors (50, 51). Alternatively, expression of the $\gamma_1$34.5 from a tumor-specific promoter has also been considered to increase replication of these oncolytic HSV vectors (50, 52).

2.6.1.4 Temozolomide (TMZ) is an oral alkylating agent approved for treatment of GBM. A phase III clinical trial demonstrated that TMZ combined with radiation therapy improved patient survival (3). Recent studies demonstrated that combinatorial TMZ + G207 HSV therapy resulted in a synergistic response and improved survival over either therapy alone in animal studies. While TMZ added to wild-type HSV-1 exhibited no synergy, it had an additive effect and importantly, was not antagonistic (53). There are no data on the effect of TMZ on $\Delta\gamma_1$34.5 capable of late viral protein synthesis and wild-type replication.

2.6.2 Increasing Viral Spread.

Viral spread in the tumor has been posited as another limitation of oncolytic virus therapy. Necrotic and ischemic regions of the tumor will not support viral replication and are thought to limit spread of the virus through the tumor (54). In the phase I clinical trial with G207, patient tumor samples showed virus infected tumor separated from uninfected tumor by necrotic regions (*J.M. Markert, unpublished data*). Convection enhanced delivery has been used with adenovirus and AAV to increase the distribution of virus through bulk flow in the tumor interstitium (55). Genetic modification such as the insertion of a fusogenic glycoprotein has also been used to enhance viral spread (56). Finally, other investigators have used multiple injections in the tumor to overcome the limitations posed by necrotic regions in the tumor (57).

2.6.3 Enhancing Bystander Toxicity

In addition to direct viral damage to the tumor, oncolytic HSV have also been used as a platform for anti-glioma gene therapy. HSV has several advantages over other viruses for gene delivery in the CNS: *i*) it is neurotropic and *ii*) its genome size (152 kb) allows transfer of genes 30 kb or more in size. Selection of the correct combination of the engineered HSV construct and gene(s) for transfer should, theoretically, allow maximal exploitation of the advantages of each technique (i.e. direct destruction of the tumor by virus replication and its cell-to-cell spread within the tumor followed by subsequent foreign

gene expression, allowing for the added destruction of any surviving tumor cells). Thus far, immunomodulatory genes (IL-12, TNF-α, CCL2, IL-4, and IL-10) and prodrug converting enzymes (purine nucleoside phosphorylase, or PNP, and cytosine deaminase, or CD), have been expressed from the virus (58-61). We have previously demonstrated that a $\Delta\gamma_1$34.5 HSV-1 expressing murine interleukin 12 (M002) prolonged survival of immunocompetent mice in an experimental intracranial murine model of neuroblastoma (58).

2.7 HSV/HCMV chimeric viruses.

In an effort to define the HCMV genes responsible for PKR-evasion, we performed marker transfer studies and constructed a series of $\Delta\gamma_1$34.5 recombinant viruses containing putative PKR-evasion genes from the β herpesvirus HCMV (**Figure 2**) (33). We hypothesized that the PKR-evasion gene from a genetically related virus would selectively complement one function of the HSV-1 $\gamma_1$34.5 gene, efficient late viral protein synthesis. However, because HCMV is only distantly related to HSV, the HCMV PKR evasion genes would not restore the neurovirulence function encoded by the HSV $\gamma_1$34.5 gene. We predicted that this selective complementation of one $\gamma_1$34.5 function (late viral protein synthesis) would enable the virus to replicate more efficiently than $\Delta\gamma_1$34.5 HSV and that this would lead to improved secondary cell infection and spread in the tumor. Studies, funded through a developmental project grant within the UAB SPORE, are described below in **Section 2.8** and show that these HSV/HCMV chimeric $\Delta\gamma_1$34.5 recombinant viruses, or chimeric HSV, are superior to first generation $\Delta\gamma_1$34.5 HSV vectors with respect to replication, expression of late viral proteins, and enhanced tumor specific killing.

2.8 Specific Findings On Safety and Efficacy of C134.

Experimental intracerebral therapy with $\Delta\gamma_1$34.5 HSV-1 is safe. However, poor replication and spread of the recombinant virus threatens to limit therapy. Modifications of these vectors have demonstrated improvements in survival in pre-clinical models of GBM. Preliminary studies have been conducted to identify whether chimeric viruses that inhibit PKR function replicate and spread in the tumor better than $\Delta\gamma_1$34.5 recombinant, and are summarized below.

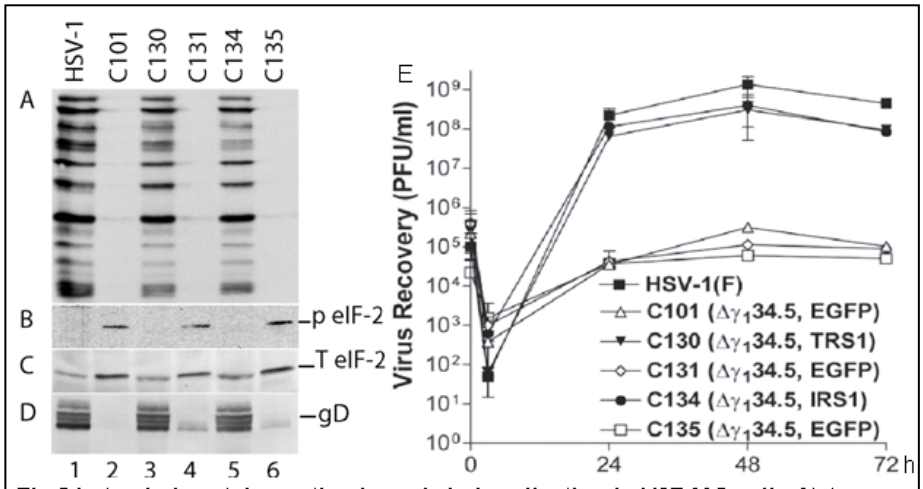
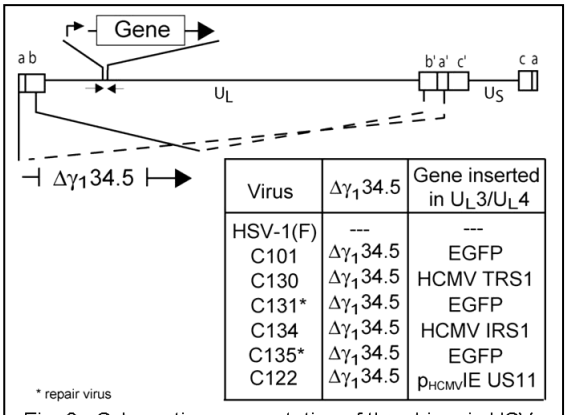


Fig 3 Late viral protein synthesis and viral replication in U87-MG cells A) Auto-radiograph of ^{35}S-Met pulse-labeled cells at 14hpi. Immunoblots showing **B**) phos-phorylated eIF-2α, **C**) total-eIF-2α, and **D**) glycoprotein D. **E**) Multistep viral replication in U87-MG cells *in vitro*.



Virus	$\Delta\gamma_1$34.5	Gene inserted in U_L3/U_L4
HSV-1(F)	---	---
C101	$\Delta\gamma_1$34.5	EGFP
C130	$\Delta\gamma_1$34.5	HCMV TRS1
C131*	$\Delta\gamma_1$34.5	EGFP
C134	$\Delta\gamma_1$34.5	HCMV IRS1
C135*	$\Delta\gamma_1$34.5	EGFP
C122	$\Delta\gamma_1$34.5	p_{HCMV}IE US11

* repair virus

Fig. 2 - Schematic representation of the chimeric HSVs (C130, C134), the repair viruses (C131, C135), and C122 ($\Delta\gamma_1$34.5, αUs11).

2.8.1. The chimeric HSV synthesize late viral proteins and replicate like wild-type virus in malignant glioma cell lines. We hypothesized that the PKR-mediated host protein shutoff response is intact in GBM cells, thus limiting $\Delta\gamma_1$34.5 viral replication. To test this hypothesis U87 MG cells were infected with 10 plaque forming units of virus per cell and at 14 hours post-infection, incubated with media supplemented with radioactive methionine for 1 hour. The pulse labeling experiments and follow up immunostaining studies for phosphorylated eIF-2α show that $\Delta\gamma_1$34.5 HSV (C101,

C131, C135) triggers PKR-mediated protein shutoff in the infected human glioma cell lines U87MG (**Figure 3A-C, lanes 2, 4, and 6**), U251MG, and D54MG (data not shown). In contrast, the chimeric HSV (C130, C134) maintain late viral protein synthesis similar to wildtype virus in these cell lines (**Figure 3A-C, lanes 1, 3, and 5**). To identify if viruses capable of synthesizing late viral proteins accumulate greater amounts of viral protein, we immunostained for viral protein glycoprotein D (gD). There was more gD in the chimeric HSV (C130 and C134) and wild-type HSV infected cells than in the $\Delta\gamma_1$34.5 infected samples (C101, C131, and C135) (**Figure 3D**). To identify if the chimeric HSV with their ability to synthesize late viral proteins, would replicate better than a $\Delta\gamma_1$34.5 HSV, we performed viral replication studies. Chimeric HSV generated 10^3-10^5 more virus than $\Delta\gamma_1$34.5 HSV in multistep replication studies (**Figure 3E**).

In summary, the PKR antiviral response is functional in malignant glioma cell lines tested thus far, and limits $\Delta\gamma_1$34.5 late viral gene expression and replication. In contrast, chimeric HSV synthesize late viral proteins, accumulate greater amounts of viral proteins, and replicate similarly to wild-type HSV-1.

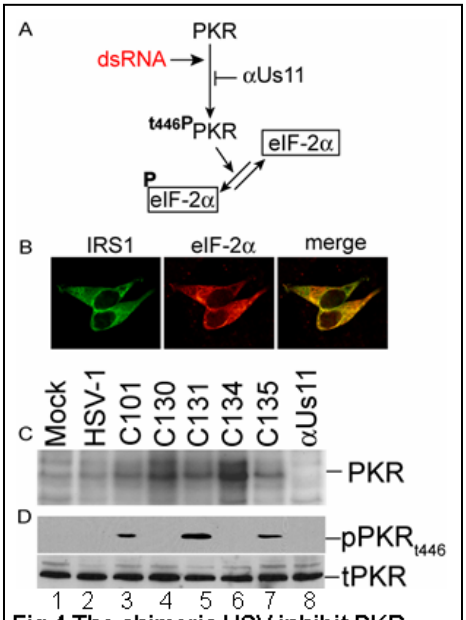


Fig 4 The chimeric HSV inhibit PKR activation. **A)** Schematic of PKR pathway **B)** Confocal microscopy showing IRS1 and eIF-2α colocalization **C)** PKR In vitro kinase assay **D)** Immunoblot with phosphospecific antibody against PKR_{T446} (upper) and total PKR (lower)

2.8.2. Mechanism of TRS1 and IRS1 inhibition of PKR. Defining how the HCMV IRS1 and TRS1 genes preclude PKR function in the cell is the focus of another proposal. However, some of this information is included to demonstrate that the chimeric HSVs encode a unique PKR evasion mechanism that may contribute to their improved anti-glioma activity.

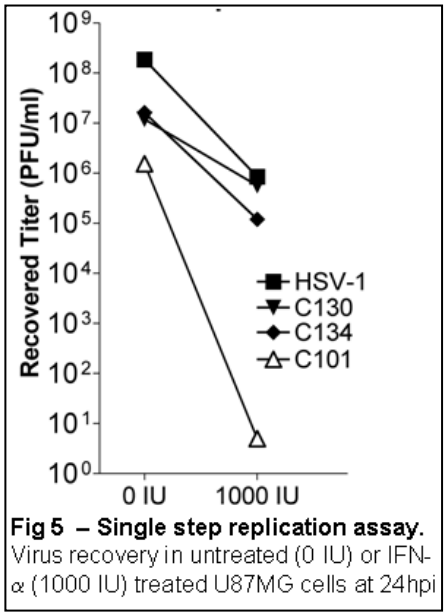


Fig 5 – Single step replication assay. Virus recovery in untreated (0 IU) or IFN-α (1000 IU) treated U87MG cells at 24hpi

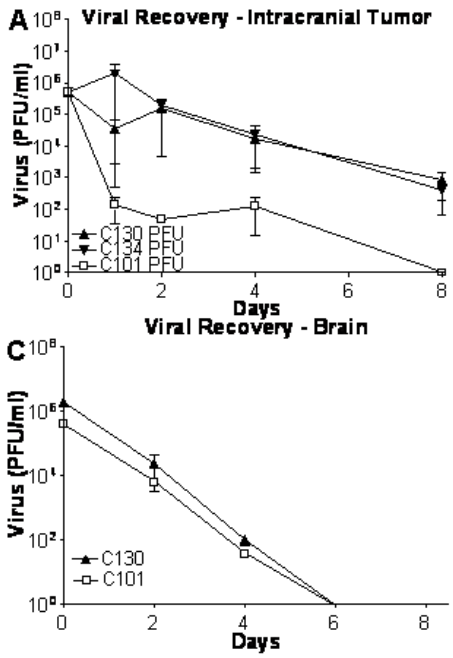
<u>IRS1 and TRS1 co-localize with the eIF-2α and prevent PKR activation in chimeric HSV infected cell lysates.</u> In reciprocal pull down studies, PKR co-precipitates with HCMV genes (data not shown). Confocal microscopy also shows that HCMV proteins co-localize with eIF-2α in infected cells (data shown for IRS1 **Figure 4B**). To test the hypothesis that IRS1 and TRS1 prevented PKR activation in the infected cell, we examined PKR phosphorylation status by *in vitro* kinase assays and immunostaining studies. These studies showed, consistent with past published results, that PKR was activated in $\Delta\gamma_1$34.5-infected samples (C101 C131, and C135), as indicated by both radioactive phosphorous labeling and detection of phospho-PKR-T446 by immunoblot (**Figure 4C, D lanes 3, 5, and 7**). In contrast, in cells infected with a αUS11 recombinant virus, PKR was maintained in its inactive or unphosphorylated state (**Figure 4C, D lane 8**). The novel findings in these studies pertain to the chimeric HSV and show that PKR, while abundantly phosphorylated in the kinase assay, remains in its inactive form, as indicated by its lack of autophosphorylation on threonine #446 (**Figure 4 C, D lanes 4 and 6**). These data indicate that TRS1 and IRS1 co-precipitate and co-localize with PKR and eIF-2α. The data also show that in the C130 and C134 infected cells, PKR remains in its non-activated form. Chimeric HSV apparently utilize a different mechanism than the αUS11 virus to block PKR activation.

2.8.3. Chimeric viruses exhibit wildtype viral resistance to Interferon α (IFN-α).

The $\gamma_1$34.5 gene product is integral to HSV-1 IFN resistance (He, 2004). Type I IFN treatment reduces $\Delta\gamma_1$34.5 replication. To identify if chimeric HSV exhibit wild-type viral resistance to Type I IFN, we examined viral replication in the presence or absence of IFN-α treatment. Single step replication

assays were performed by infecting U87-MG with an excess of virus (10 PFU/cell) and evaluating a single round of virus replication. In these single step replication assays **(Figure 5)**, minimal $\Delta\gamma_1$34.5 virus was recovered (6 PFU/ml) in interferon-treated cultures. Chimeric recombinants replicated similarly to wildtype virus, generating 10^5-10^6 PFU/ml of virus in IFN-treated samples **(Figure 5)**.

In summary, chimeric HSVs, like HSV-1(F) replicate despite IFN-α treatment and are anticipated to infect secondary tumor cells better than $\Delta\gamma_1$34.5 virus *in vivo*.



B **Neurotoxicity – LD_{50}**

Virus	LD_{50}
HSV-1	75
G207 ($\Delta\gamma_1$34.5, ΔUL39)	>3 x $10^{8\#}$
C101 ($\Delta\gamma_1$34.5)	>1 x10^7
C130 ($\Delta\gamma_1$34.5, TRS1)	6.8 x 10^5
C122 ($\Delta\gamma_1$34.5, αUs11)	8.3 x10^5
C134 ($\Delta\gamma_1$34.5, IRS1)	>1 x 10^7

#based upon historical data

Fig 6 – I*n vivo* viral recovery studies from mouse brain with or without U87 tumors and Neurotoxicity studies – **A)** Infectious virus and Taqman quantitative PCR from U87 xenografts tumors inoculated with 5 x10^5 pfu of C130, C134 or C101 **B)** LD_{50} values of wild-type HSV, chimeric HSV and repair viruses **C)** Virus recovery from the brains of CBA mice inoculated with C101 or C130 virus.

2.8.4. The chimeric HSV replicate better than $\Delta\gamma_1$34.5 in intracranial tumors. To determine whether chimeric HSV replicated better than $\Delta\gamma_1$34.5 virus in intracranial tumors, we implanted U87-MG tumors in nude mice, treated them with 5 x 10^5 PFU of virus and examined virus recovery on days 1, 2, 4, and 8 post-infection. Results showed increased chimeric HSV recovery (~10^3 PFU higher recovery) and a greater duration of viral replication (C134 and C130 >8d vs $\Delta\gamma_1$34.5 >4d) in U87 xenografts compared to an equivalent dose of $\Delta\gamma_1$34.5 HSV (**Figure 6A).**

2.8.5. The chimeric HSV do not exhibit wild-type neurovirulence. The $\gamma_1$34.5 gene encodes at least three phenotypes pertinent to anti-tumor therapy: (1) evasion of PKR-mediated host protein shutoff response, (2) Type I IFN resistance and (3) neurovirulence. As described above, the HCMV TRS1 and IRS1 genes restore at least two of the $\gamma_1$34.5 gene functions, viral evasion of the PKR host protein shutoff response and resistance to IFN-α.

To determine if the HCMV TRS1 and IRS1 gene restored neurovirulence, we performed lethal dosage measurement (LD_{50}) studies, as described previously (27). As indicated (**Figure 6B),** introduction of the IRS1 gene (C134) into a $\Delta\gamma_1$34.5 HSV background did not contribute to neurovirulence. The $\Delta\gamma_1$34.5 parent virus C101 and the IRS1 expressing chimeric recombinant C134 have identical neurotoxicity profiles (>1 x 10^7). In contrast, insertion of the TRS1 gene (C130) or αUS11 gene (C122) into $\Delta\gamma_1$34.5 HSV partially restores neurovirulence, but only approximately 15 fold (C130 LD_{50} = 6.8 x 10^5, C122 LD_{50}=8.3x10^5). This is within the LD_{50} range of the $\Delta\gamma_1$34.5 HSV (HSV 1716) used in Phase I trials (62). While chimeric HSV were safe in neurotoxicity studies, it was still possible that they were capable of replication and could be producing subclinical CNS damage in the mice. To identify if chimeric HSV replicated better than $\Delta\gamma_1$34.5 HSV in the CNS, we intracranially inoculated mice with equivalent PFU of C101 and C130 and found that the two recombinants replicate similarly in non-malignant CNS (**Figure 6C**). It is important to note that chimeric HSV retain sensitivity to antiviral therapy with acyclovir (ACV) (data not shown).

In summary, the HCMV TRS1 or IRS1 genes restore wildtype viral protein synthesis and replication in malignant glioma cells, but do not restore wildtype neurotoxicity. Insertion of the HCMV TRS1 gene increases virulence of $\Delta\gamma_1$34.5 chimeric C130 slightly, but C134 ($\Delta\gamma_1$34.5, IRS1) chimeric recombinant is as safe as other $\Delta\gamma_1$34.5 HSV. Both of these chimeric HSV retain susceptibility to ACV therapy.

2.8.6. Chimeric HSV reduce tumor volumes *in vivo*. To identify if chimeric HSV was more effective than $\Delta\gamma_1$34.5 virus at reducing tumor volume, we induced U251-ffLuc intracranial tumors in *scid* mice (1 x 10^6 cells), and treated the animals with a chimeric HSV (C130), a $\Delta\gamma_1$34.5 recombinant (R3616), or saline a week later. We then measured luciferase activity over time using a xenogen *In Vivo* Imaging System (IVIS; **Figure 7A**). The method involved implantation of GBM cells stably expressing firefly luciferase enzyme and at selected times post implantation or post-virus administration, intraperitoneal administration of a luciferase substrate (beetle luciferin, 2.5mg/mouse) to the hosts. This low molecular weight (~1kD) substrate, upon entering cells containing luciferase enzyme, is cleaved into a photo-emitting chemical by an ATP-dependent process and then is rapidly degraded (63). Llight emitted is captured digitally by a Xenogen IVIS CCD camera and quantified. Because luciferase enzyme is not present in native animal cells and has a limited half-life at 37ºC of about 2 hrs, light emission is limited to viable, metabolically active tumor cells (63). The greater the number of viable GBM cells, the greater the light production. Consistent with prior studies, these results showed that $\Delta\gamma_1$34.5 therapy (R3616) reduced tumor volume (based upon relative photon emission) when compared with saline treated animals, but that the chimeric HSV (C130) was more effective at reducing tumor volume (**Figure 7A**).

2.8.7. Chimeric HSV therapy improves survival in both a GBM xenograft and syngeneic murine brain tumor model. Since the chimeric HSV demonstrated both improved replication and protein synthesis phenotype, we hypothesized that this would translate into improved survival of mice treated with either C130 or C134 chimeric HSV versus conventional $\Delta\gamma_1$34.5 HSV treatment. To test this hypothesis, cohorts of *scid* mice bearing U87-MG intracranial tumors were treated with saline or equivalent doses (5×10^5 pfu) of $\Delta\gamma_1$34.5 or chimeric HSV. As shown in **Figure 7B,** direct intratumoral injection of C130 and C134 chimeric HSV improved survival of mice versus treatment of tumors with C101 or G207 ($P < 0.0001$). Though C101 statistically improved survival over saline treated mice as expected, ultimately all of the C101-treated animals died. In contrast, the majority of animals treated with chimeric HSV at a matched dose survived.

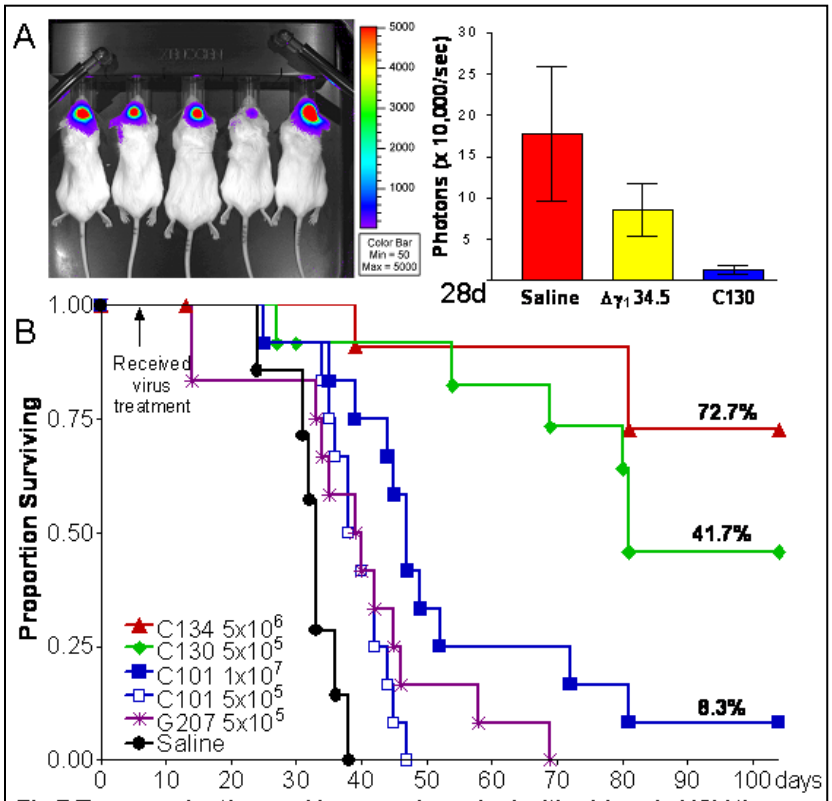


Fig 7 Tumor reduction and improved survival with chimeric HSV therapy. **A)** Detection of luciferase activity in C.B-17 *scid* mice bearing U251MG-*ffLuc* Gliomas (left). Chimeric HSV produces a statistically significant reduction in IC tumor volume as measured by photon emission from U251-*ffluc* tumors 28d post-treatment with saline or 2 x 10^5 PFU $\Delta\gamma_1$34.5 or chimeric HSV (right). **B)** Kaplan-Meier curve showing survival after treatment with virus 7d after implantation of 1x10^6 U87-MG tumor cells in the CNS of SCID mice

Poorly replicating $\Delta\gamma_1$34.5 HSV-1 derives a greater benefit from dose escalation than chimeric HSVs. Administration of a higher dose of C101 significantly improved median survival of the mice ($1x10^7$ [45d] vs. 5×10^5 pfu [36.5d], $P < 0.0001$). Chimeric HSV were even more effective at lower doses than the maximum administered dose of the $\Delta\gamma_1$34.5 virus (5×10^4 PFU of C130 - >50% of the animals survived vs 1×10^7 PFU C101- 15% survival, $P = 0.0185$). A similar benefit was witnessed in the syngeneic Neuro2A brain tumor model, where chimeric HSVs (C130 and C134) were superior to $\Delta\gamma_1$34.5 therapy and an αUs11 HSV, yielding a 15-20% improvement in median survival (p=0.0039).

To summarize, chimeric HSV were superior to $\Delta\gamma_1$34.5 HSV in two separate experimental murine brain tumor models. Chimeric HSV significantly improved survival over all $\Delta\gamma_1$34.5 HSV-treated cohorts in the human xenograft brain tumor model. They also improved survival over treatment with $\Delta\gamma_1$34.5 HSV or an αUS11 recombinant in a syngeneic murine brain tumor model. Due to its high level of efficacy and low neurovirulence profile, C134 demonstrates the most advantageous therapeutic ratio, a critical determinant for its utility in patients.

2.8.8. Effect of IR upon HSV replication. Preliminary studies show that administration of 5 Gy of IR to the infected tumor bed improves viral replication and survival. Optimal timing of IR is between 6 and 24 hpi (data not shown). Preliminary data indicate that in a U87-MG xenograft model, irradiation (5Gy) of G207 infected tumors improved long term survival from ~15% to 60% when performed 24hpi **(Figure 8A)**. Interestingly, administration of IR at 4hpi and 120 hpi did not result in a statistically significant improvement in survival **(Figure 8A)**. Preliminary studies have identified a "therapeutic window" between 6h and 24h post-infection where IR benefits viral replication and leads to a synergistic improvement in survival. Importantly, IR administered outside of this therapeutic window, while not enhancing viral oncolysis, is not detrimental to viral therapy. Additional studies have shown that the benefit derived by IR is not limited to $\Delta\gamma_1$34.5 viruses. Recombinants encoding a single $\gamma_1$34.5 gene replicate better following IR. Furthermore, preliminary studies show that external beam IR improves HSV-1(F) replication in flank tumors (~1 log increase in recovered virus, data not shown). Addition of IR to G207 therapy is currently in a SPORE-sponsored Phase I clinical trial, with 8 patients enrolled thus far (**Figure 8B**).

In summary, IR enhances viral protein synthesis and replication and in an intracranial xenograft model has been shown to improve outcome when administered within 6-24 hours of G207 therapy.

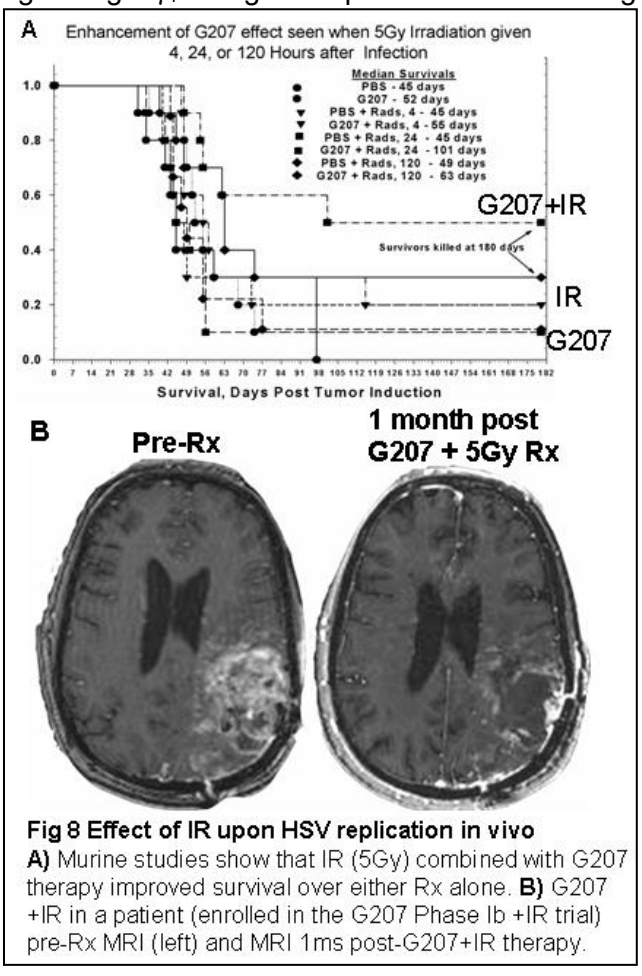


Fig 8 Effect of IR upon HSV replication in vivo
A) Murine studies show that IR (5Gy) combined with G207 therapy improved survival over either Rx alone. **B)** G207 +IR in a patient (enrolled in the G207 Phase Ib +IR trial) pre-Rx MRI (left) and MRI 1ms post-G207+IR therapy.

2.8.9. Stability of Optiprep HSV vectors

Convection enhanced delivery (CED) requires prolonged infusion of the virus through a catheter into the tumor. To evaluate the stability of Optiprep recombinant virus, we placed equivalent PFU of virus in catheters at 4ºC and at 37ºC and measured the quantity of virus recovered over time by plaque reduction assay. Results showed that Opti-prep purified HSV is relatively stable at 37ºC with a calculated half-life of 16.5h (6.8×10^9pfu @ 0h vs $9x10^8$pfu @ 48h).

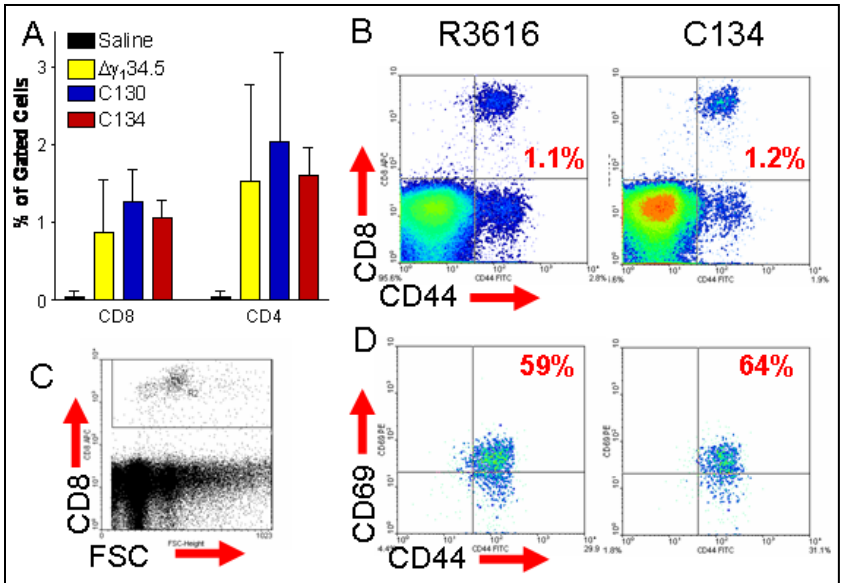


Fig 9 – Flow cytometry of brain mononuclear cell infiltrates from CBA mice 11d after IC injection with 5x10^5 pfu of virus. A) Similar CD4+ and CD8+ lymphocyte responses are seen in mice infected with $\Delta\gamma_1$34.5 (R3616) or chimeric HSV (C134). **B)** Representative example of the CD8+ population in R3616 and C134 infected brains. **C)** Example of the CD8 gating used for the CD69 (activation status studies). **D**) Infiltrating CD8+ lymphocytes are CD69+ indicative of activation.

2.8.10. Similar inflammatory infiltrates are detectable in the brains of CBA mice infected with chimeric HSV or $\Delta\gamma_1$34.5. As indicated in the **BACKGROUND** section, the antiviral immune response contributes to the anti-tumor effect but may also limit viral replication and spread. To identify if chimeric HSV elicit a greater immune response than $\Delta\gamma_1$34.5 recombinants, we examined immune cell infiltrates in brains of CBA mice injected with these recombinant viruses. Results showed chimeric HSV and $\Delta\gamma_1$34.5 (R3616) recombinants elicited similar inflammatory responses (**Figure 9A & B)**. The majority of CD8+ lymphocytes in the CNS were activated (CD69+), irrespective of which recombinant is injected (**Figure 9C & D**).

2.8.11. Monitoring tumor volume, viral replication/spread, and inflammatory changes *in vivo*.

a.Tumor volume. Both direct (histology) and functional measurement (animal survival) of tumor volume have been used to monitor response to oncolytic therapy (as shown in **Figures 7C, 10C & D**). These methods involved killing representative animals to evaluate interim responses, which increased animal numbers required for statistical evaluation. This approach assumes that an individual animal will reflect the population as a whole. As shown in **Figure 7C**, measurement of luciferase activity in the tumor provides an alternative method to evaluate tumor volume noninvasively, allowing longitudinal population-based analysis of therapy.

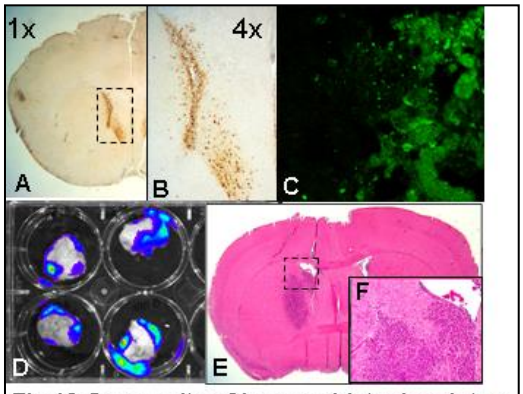


Fig 10 Composite of Immunohistochemistry (IHC), Reporter Gene Detection, and Tumor Histology A) IHC of C122 infected brain **B)** Enlarged view of HSV-infected cells (Brown) in the brain from a C122 infected CBA mouse **C)** confocal fluorescent microscopy showing EGFP expression in M2001 (wild-type HSV expressing EGFP) infected N2A flank tumors frozen sections. **D)** Xenogen IVIS detection of luciferase expressing virus in flank tumor following excision and bathing in ATP/ luciferin solution **E)** Hematoxylin and Eosin staining of a 4C8 glioma in the brain of B6D2F1 mouse 21d after injection of tumor cells **E)** higher magnification of the medial aspect of the caudate putamen showing spread toward right ventricle

b.Viral detection. Viral recovery and immunohistochemistry have been used successfully to monitor viral replication and spread *in vivo* (as demonstrated in **Figures 6A [replication] and 10A, B [IHC]**). Bioluminescent and fluorescent protein expression by the virus can also be used to indirectly monitor viral replication and spread in the tumor as demonstrated using a $\Delta\gamma_1$34.5 luciferase expressing virus (M007) and a wild-type, EGFP expressing virus (M2001) in flank tumors (**Figure 10C & D**). We routinely construct recombinant viruses to encode reporter genes (d_2EGFP, dsRED monomer, or firefly luciferase). These genes not only facilitate screening and selection of recombinant viruses *in vitro* but allow indirect monitoring of viral activity in *in vivo* studies.

2.8.12. Summary. Chimeric HSV evade a principal component of the innate immune response, PKR-mediated

protein shutoff. They replicate and resist Type I IFN similar to wildtype HSV-1 in malignant glioma cells. However, they do not exhibit wildtype neurotoxicity and, in the case of C134, are no more virulent than a $\Delta\gamma_1$34.5 HSV.

Due to its high level of efficacy and low neurovirulence profile, C134 demonstrates the most advantageous therapeutic ratio, a critical determinant for its utility in patients. Preliminary *in vivo* studies in a glioma xenograft murine model demonstrate that chimeric HSV significantly improved survival and required two to three log lower doses than $\Delta\gamma_1$34.5 therapy. Chimeric HSV, by virtue of their near-wildtype replication, efficiently spread through tumor and reduce tumor burden by direct viral oncolysis, thus improving survival. Chimeric HSV, unlike conventional $\Delta\gamma_1$34.5 HSV recombinants, maintain protein synthesis in infected cells. Chimeric HSV exhibit benefits of both an oncolytic agent and gene therapy vector by combining improved viral replication with enhanced viral protein expression.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically or cytologically confirmed recurrent/progressive glioblastoma multiforme, anaplastic astrocytoma, or gliosarcoma.

3.1.2 Prior therapy. Patients must have failed external beam radiotherapy to the brain at least 4 weeks prior to enrollment.

3.1.3 Age ≥18 years. Because no dosing or adverse event data are currently available on the use of C134 in patients <18 years of age, children are excluded from this study but will be eligible for future pediatric phase 1 single-agent trials.

3.1.4 Karnofsky Performance Status ≥70% (see Appendix A).

3.1.5 Life expectancy of greater than 4 weeks.

3.1.6 Patients must have normal organ and marrow function as defined below:

- leukocytes ≥3,000/ μl
- absolute neutrophil count ≥1,500/ μl
- platelets ≥100,000/ μl
- total bilirubin within normal institutional limits
- AST(SGOT)/ALT(SGPT) ≤2.5 X institutional upper limit of normal
- Creatinine within normal institutional limits

OR

- creatinine clearance ≥60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.

3.1.7 Residual lesion must be ≥1.0 and < 5.5 cm in diameter without bilateral extension through the corpus callosum as determined by MRI as this is a locally delivered treatment. These parameters will be re-evaluated on imaging done on the day of catheter implantation and if the lesion no longer meets the criteria, the patient will not undergo catheter implantation or treatment with C134.

3.1.8 The effects of C134 on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception prior to study entry and for the first six months after receiving C134. Because it is currently unknown if C134 can be transmitted by sexual contact, a barrier method of birth control should be employed. Should a woman become pregnant while participating in this study, she should inform her treating physician immediately.

3.1.9 Ability to understand and the willingness to sign a written informed consent document.

3.1.10 Females of childbearing potential must not be pregnant; this will be confirmed by a negative serum pregnancy test within 14 days prior to starting study treatment.

3.1.11 Steroid use is allowed as long as dose has not increased within 2 weeks of scheduled C134 administration whenever possible, the patient should be on a steroid dose that is equivalent to a dexamethasone dose of ≤ 2mg daily at the time of treatment.

3.2 Exclusion Criteria

Patients who have had chemotherapy, cytotoxic therapy, immunotherapy or gene therapy within 6 weeks prior to entering the study (4 weeks for Temodar/Temozolomide), surgical resection within 4 weeks prior to entering the study, or have received experimental viral therapy at any time (e.g., adenovirus, retrovirus or herpesvirus* protocol). Also, those who have not recovered from adverse events due to therapeutic interventions administered more than 4 weeks earlier.

3.2.1 Patients may not be receiving any other investigational agents.

3.2.2 History of allergic reactions attributed to compounds of similar biologic composition to C134.

3.2.3 Tumor involvement which would require ventricular, brainstem, basal ganglia, occipital lobe, or posterior fossa inoculation or would require access through a ventricle in order to deliver treatment.

3.2.4 Prior history of encephalitis, multiple sclerosis, or other CNS infection.

3.2.5 Active oral herpes lesion.

3.2.6 Concurrent therapy with any drug active against HSV (acyclovir, valaciclovir, penciclovir, famciclovir, ganciclovir, foscarnet, cidofovir).

3.2.7 Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or any other medical condition that precludes surgery. Also, psychiatric illness/social situations that would limit compliance with study requirements.

3.2.8 Required steroid increase within 2 weeks of scheduled C134 administration. When possible, the patient should be on a dexamethasone equivalent dose of ≤ 2mg daily at the time of treatment.

3.2.9 Known history of allergic reaction to IV contrast material that is not amenable to pre-treatment by UAB protocol.

3.2.10 Have a pacemaker, ferro-magnetic aneurysm clips, metal infusion pumps, metal or shrapnel fragments, or certain types of stents.

3.2.11 Received Bevacizumab (Avastin) therapy within 4 weeks of scheduled C134 administration.

3.2.12 Excluded patient groups

Pregnant women are excluded from this study because C134 is a viral oncolytic therapy with unknown potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with C134 breastfeeding should be discontinued if the mother is treated with C134.

Immune deficient, because patients with immune deficiency will be unable to mount the anticipated immune response underlying this therapeutic rationale, HIV-seropositive patients are excluded from this study. Other treatment studies for this disease that are less dependent on the patients' immune response are more appropriate for HIV-seropositive patients.

Unwilling/unable to receive required ophthalmologic exams

3.2.13 Any other reason the investigator deems subject is unfit for participation in the study

3.3 Inclusion of Women and Minorities

Both men and women and members of all ethnic groups are eligible for this trial. The proposed study population, assuming the maximum number of patient enrollments occurs, is illustrated in the table below.

Gender	Asian or Pacific Islander American Indian or Alaskan Native	*Black, not of Hispanic Origin	Hispanic	White, not of Hispanic Origin	Other or Unknown (Non-white)	Total
Female		1	1	8		10
Male		1	0	13		14
TOTAL		2	1	21		24

4. TREATMENT PLAN

4.1 C134 Administration

Treatment will be administered on an inpatient basis. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Patients will be treated under monitored local anesthesia, or at the surgeon's discretion, under general anesthesia. After placement of the stereotactic frame, the patients will then undergo a contrasted MRI scan to determine the site for stereotactic biopsy. Patients will then undergo stereotactic biopsy of their tumor. While evidence of radiation damage or necrosis may be present on the frozen section, inoculation with C134 will only proceed if viable, recurrent glioma is also present on the frozen section. The initial dose level of C134 will be 1×10^6 plaque forming units (pfu). Dosing modifications will be undertaken by the Continual Reassessment Method outlined in 4.1.1. Virus will be inoculated via catheters placed stereotactically in enhancing regions of tumor at up to 5 different loci (each injection over 2 minutes). Catheters will be removed directly after administration.

Virus will be thawed and maintained on ice until ready for delivery; a total of 5.25 hours from thawing to delivery has demonstrated titer stability (4 hours at 2-8 degrees Fahrenheit followed by 1.25 hours at ambient temperature).

4.1.1 Continual Reassessment Method

Dr. Gary R. Cutter and Dr. Inmaculada B. Aban, Professors in the Department of Biostatistics, UAB School of Public Health, with expertise in CRM calculations will apply the software developed by Dr. Steven Piantadosi, (Cedars-Sinai) who will serve as a clinical trial statistical consultant to advise and assist in the implementation of the Continual Reassessment Method in determining dose alterations. In addition, Drs. Aban and Cutter, will provide support in clinical trial and data management, and data analysis.

Rationale for the Use of a Modified Continual Reassessment Method: The description of the determination of MTD from the CRM that we are employing is adapted from that used previously in a Phase I/II study of the poly (ADP-ribose) polymerase-1 (PARP-1) inhibitor BSI-201 in patients with

newly diagnosed malignant glioma conducted under the New Approaches to Brain Tumor Therapy (NABTT) CNS Consortium. To estimate the MTDs in terms of clinical toxicities, a modified continual reassessment method (CRM), based on that described by Piantadosi et al (64)], will be employed. The CRM has been shown to be less biased and more efficient for estimating the MTD than traditional dose-finding models. The efficiency of the CRM stems from its explicit use of biological knowledge in the form of a parametric dose toxicity model. In the CRM, only a starting dose is specified and the dose is escalated or deescalated based on the toxicities of the previous cohort.

This is advantageous because the investigators can choose the next dose level based on all available clinical and statistical information rather than on relatively arbitrary predetermined doses. One disadvantage of the CRM is uncertainty of the dose levels that will be used in the trials, because the specific dose levels are not defined at the start of the trial.

Details of CRM Design: The primary statistical outcome for this study is the occurrence of serious clinical toxicity. Investigators would like to employ a dose of drug that yields approximately a 1/3 chance of serious toxicity. In our opinion, this represents the best chance at a beneficial therapeutic ratio for this unusually difficult disease to treat. This target probability of toxicity is chosen based on knowledge of previous trials of oHSV in glioma, but is fundamentally subjective. The relationship between dose of drug and probability of toxicity is assumed to follow a two-parameter logistic model, both before and during the dose finding given by where β is the "slope" of the curve and d50 the midpoint (or dose that yields a 50% response). The parameters β and d50 govern the dose finding process, and are estimated, denoted by and, initially by clinical judgment and afterwards by the observed data. This represents a second subjective component of dose finding designs. Classical dose-ranging designs incorporate this component of subjectivity by setting out, in advance of the experiment, a set of doses to employ. A strictly Bayesian approach to the CRM requires a joint prior probability distribution for the parameters β and d50. However, we have found it easier for clinicians to render their clinical judgment about β and d50 in the form of pseudo-data. Specifically, we ask for two points on the dose toxicity curve: the dose thought to yield a 10% probability of toxicity (d10) and the dose thought to yield a 90%probability of toxicity (d90). Two points, d10, d90, are required to initiate the fit for a two-parameter model. The exact points chosen are arbitrary, but we have found these generally work well or are easily adapted. The d10 point can often be discarded after some data have been obtained. The d90 point is necessary to obtain a fit of the model, but is usually relatively unimportant because it characterizes a region of the model that does not heavily influence prediction of the next dose. In this sense, d90 is a nuisance parameter – necessary for model fitting, but relatively uninfluential on the dose escalation. At both d10 and d90, the investigator specifies a numerator (number of responses) and denominator (number of subjects treated), such that numerator/denominator = 0.1 or 0.9 as the case may be. The denominators are always taken to be small numbers, e.g. 1, to represent weak evidence and reduce the influence of these points compared to real subject data. Three values for d90 will be chosen in this protocol with weights of one tenth that of real subject data. This allows flexibility in the upper end of the dose toxicity curve. This adaptation to the CRM came about after subject data demonstrated that d90 was incorrect in previous studies, because doses approaching d90 were tried with no toxicities observed. This situation required that d90 be moved to a higher dose or the fitted dose toxicity curve became too steep and no dose escalations resulted. We assume the dose for d10 = 1 x 10^4 pfu for C134 (Table 1). A set of three values will be chosen for d90 =1 x 10^{15} pfu. These values for d90 spread probability mass over a wider range and may eliminate the need to these starting points, our desire is to employ a dose of virus to yield no more

$$P(toxicity|dose) = \frac{1}{1 + e^{-\beta(dose - d_{50})}}$$

Eqn. (1)

Table 1: Initializing Data used to start the CRM

Log Dose	N	r	Weight
4	1	0.05	0.5
5	1	0.10	0.5
6	1	0.2	0.5
7.5	1	0.5	0.5
9	1	0.8	0.5
10	1	0.9	0.5
12	1	1	0.5
15	1	1	0.5

(Initial recommended dose based on these data=6.7842)

than 33% chance of clinical toxicity. The initial starting dose will be assumed to be 1 x 10^6 PFU and the maximum dose to be tested would be 1 x 10^8 PFU. Further assumptions would be that the maximum number of subjects would be 24 and that the dose cohort size would be 1. Further, the next CRM recommended log dose would be rounded to the nearest 0.5 or full dose. Moreover, the number of consecutive subjects at the maximum tolerated dose would be 10 or a number until 24 subjects are treated, whichever comes first. This will allow us to collect more information of the safety of the MTD. If a second toxicity is observed for patients on the highest dose, then the next lower dose is used and declared MTD if 10 consecutive subjects on the same dose are toxicity free or if n=24 is reached. If more toxicities are found, CRM will be used in the de-escalation of the dose. For each subsequent level, the investigators will evaluate the recommended dose-level. It is possible that the model may recommend large interval increases in dose level with which the investigators do not feel comfortable. In these cases, the investigators will use this information and their best clinical judgment to assign a next dose level. We emphasize that the dose levels recommended by the CRM should not be taken literally.

Model based dose escalation methods, especially the CRM, are able to account for ordinal or quantitative toxicity assessments, and use this information to guide subsequent dose changes. In particular, the binomial likelihood is:

Eqn. (2)

$$L(\beta, d_{50}) = \sum_{i=1}^{k} \left[\log \binom{n_i}{r_i} - n_i \log\left(1 + e^{-\beta(d_i - d_{50})}\right) - (n_i - r_i) \log\left(1 + e^{-\beta(d_i - d_{50})}\right) \right]$$

where i indexes the dose level, p is the probability of toxicity (equation 1 above), d is dose, n the number of subjects treated at each dose, and r the number of toxicities. While n is constrained to be an integer, r does not have to be integral. In particular, r can be taken to be the sum of ordinal or quantitative toxicity measures provided that r < n. The maximization of equation 2 with respect to the parameters (model fitting) can then proceed in the usual fashion. Furthermore, the ordinal scores need not be the same for all types of toxicity. For example, we might not want alopecia to have the same effect on dose reduction as neurologic toxicities.

As subjects are treated at doses estimating the true MTD, the recommended subsequent dose levels will begin to converge. The criteria to declare the MTD will be when 2 recommended doses are within 10% of one another. It is possible that the dose escalation could continue indefinitely and that the MTD is not reached. If 10 subjects are treated in the full dose range in this dose-finding study and the MTD has not been reached, we will take pause, evaluate the data, and determine whether to continue the dose-escalation or terminate the Phase I portion of the study. If a MTD is not being reached based on clinical toxicities (too many or too few), the biological indicator (increased PFS or OS) may factor in the choice of the C134 dose for the ultimate planned phase II trial. A maximum of 10 subjects will be treated at the putative MTD to have better estimation of ≤ 33% DLT rate.

4.1.2 Estimated Number of Patients

We anticipate as few as four and as many as 24 patients could be enrolled in this trial). If the highest planned dose is successfully administered to subjects and an additional 9 subjects will be entered at the CRM-estimation of the safe target dose, there could be as few as 16 patients (Table 2: Scenario 1) or as

Table 2: Enrollment Scenario Examples

Subject #	S1	S2	S3	S4
1	6	6	6	6
2	7	7	7	7
3	7.5	7.5	7.5	7.5
4	8	8	8	8
5	8	8	8	8
6	8.5	8.5	8.5	8.5
7	9	9	9	9
8	9	8.5	9	9
9	9	8.5	9	9
10	9	8.5	9	8
11	9	8.5	9	8.5
12	9	8.5	9	8.5
13	9	8.5	9	8.5
14	9	8.5	9	8.5
15	9	8.5	8.5	8.5
16	9	8.5	8.5	8.5
17		8.5	8.5	8.5
18			8.5	8.5
19			8.5	8.5
20			8.5	8.5
21			8.5	
22			8.5	
23			8.5	
24			8.5	
MTD	9	8.5	8.5	8.5

White Cells = No Toxicity
Magenta Cells – Toxicity
MTD = Maximum Tolerated Dose

many as 24 patients treated (Table 2: Scenario 3). If, on the other hand, all subjects develop DLTs, the CRM model would de-escalate both through the initial and two lower dose levels involving no more than 4 subjects and the trial would be halted (Section 4.5) with a minimal accrual of 4 subjects. Examples of enrollment scenarios following a DLT but leading to an MTD dose determination are shown in Table 2: S2-4). **Please note that while Table 2 suggests that a dose of 10^9 pfu might be considered, this will not be utilized without a revised protocol from the FDA as our current IND only permits dosing up to 10^8 pfu.**

Please note the table and the enrollment scenarios are examples only and do not represent all possible scenarios.

4.2 Dose-Limiting Toxicity

The Cancer Therapy Evaluation Program (CTEP) has published Common Toxicity Criteria for the grading of adverse events experienced in clinical trials for anti-neoplastic agents. As defined by this criteria, any Grade 3 or 4 toxicity involving the liver, lungs and heart, or any other Grade 4 toxicity, will be considered a dose-limiting toxicity (DLT) if it is determined to be possibly, probably, or definitely related to C134. Because of the site of C134 inoculation, important additional events that will be considered dose-limiting toxicities if they are possibly or probably related to C134 include death, stroke, hematoma requiring surgery, untreatable neurologic deterioration, unresponsive systemic infection, and disseminated HSV infection. All adverse events will be reported to the Data and Safety Monitoring Board (DSMB) for determination of attribution and dose-limiting toxicity.

Management of the above adverse events is outlined in Section 5.

Dose escalation will proceed according to the CRM scheme, described above.

The maximally tolerated dose (MTD) is the highest dose level below the maximally administered dose when dose escalation decisions are made according to the guidelines above.

4.3 Supportive Care Guidelines

There will be a minimum seven-day observation period between each patient enrolled to allow for evaluation of potential toxicity. If the incidence of DLT at any given dose level meets the criteria for dose escalation, there will be a waiting period of 24 days before dose escalation occurs. The Medical Monitor in conjunction with the UAB Comprehensive Cancer Center Data Safety Monitoring Panel will evaluate the safety of each dose tested to determine whether the protocol may proceed to the next dose level. An independent Data and Safety Monitoring Board (DSMB) will be assembled to assess the progress of the C134 study, the safety data, and critical efficacy endpoints (when appropriate) and provide recommendations to the IND investigator sponsor. The DSMB will review study data in a cumulative fashion (including but not limited to adverse events) to evaluate safety, conduct of the study when appropriate, as well as the scientific validity and data integrity of the study.

Supportive Care Guidelines

Appropriate supportive care during the duration of the study includes the following:

- Steroid administration for neurologic symptoms arising from increased edema or intracranial pressure
- Proton pump inhibitors or H2 antagonists for control of steroid-induced gastric irritation

- Anti-epileptic medicines for control of partial or generalized seizures
- Post-operative neurological intensive care that is routine for the neurosurgical interventions involved in the administration of C134
- Other than a restriction on medications with anti-HSV activity (to be given only for the management of an adverse event), there are not any limitations on concomitant medications that patients may receive for other co-morbidities.

Management of adverse events is discussed in Section 5.

4.4 Duration of Therapy/Study

The therapeutic intervention in this trial involves the administration of a single dose of C134. For this reason it is more appropriate to define the duration of the study for each patient rather than the duration of therapy. Following the 12-month study period described in Section 8.0, patients administered C134 will be subject to long term follow-up (15 years)via annual examinations to detect potential delayed adverse events.

In regard to the evaluations of treatment efficacy or the acceptability of other treatments for the malignant glioma, the study will continue as scheduled until one of the following criteria applies:

- Disease progression (as defined in Section 9)
- Patient withdrawal from the study

Scheduled post-therapy safety evaluations as indicated in the study schedule will continue for every patient regardless of the response to C134. These evaluations will stop only if one of the following criteria applies:

- Disease progression (as defined in Section 9) has rendered the patient unevaluable
- Patient withdrawal from the study

5. EXPECTED ADVERSE EVENTS/DOSE MODIFICATIONS

5.1 Expected Adverse Events Associated with Malignant Glioma

Subjects in this trial may present with various adverse events due to their underlying disease. The table below outlines various expected adverse events. These events will not be considered stopping criteria unless the severity is a Grade 4 or higher or unless otherwise indicated. In the event the severity is a Grade 4 or higher, the trial will be halted until review by the Data and Safety Monitoring Board. The DSMB will make a determination as to the attribution of the adverse event to the study drug, study procedure, or underlying disease as well as to whether the study may proceed.

Expected Adverse Events due to Disease

Asthenia	Amnesia	Nausea	Somnolence	Leukopenia
Fever	Pneumonia	Death*	Hemiplegia	Confusion
Headache	Decreased Consciousness	Anemia	Cachexia	Varicella Zoster Infection
Abnormal Mentation	Stroke	Dysphasia	Depression	Deep Vein Thrombosis
Seizure	Abnormal Erythrocytes	Urinary Tract Infection	Tumor Progression or pseudoprogression	Increase Liver Transaminases

Hematoma	Encephalitis/Encephalopathy*	Hepatitis	Nuchal Rigidity	Photophobia
*Occurrence of these events meets stopping criteria and will halt the trial until evaluation by the DSMB.				

Patients will be observed closely for evidence of any adverse events. After the delivery of C134 , patients will initially be observed in the Neurosurgical Intensive Care Unit. The patients' vital signs (temperature, blood pressure, pulse, respiratory rate) and neurologic function (Glascow Coma Scale and limited neurological exam) will be monitored every hour for the first six hours, then every two hours overnight for the first 24 hours. Patients that appear stable will then be transferred to the neurosurgery ward or the General Clinical Research Center, during which time the frequency of monitoring will be determined by the attending physician(s) based on the medical condition of the patient.

After discharge the patient will continue to be closely followed for evidence of adverse events, with outpatient follow-up evaluations scheduled at 1, 3, 6 and 12 months, or more often if medically indicated. The safety evaluation schedule is outlined in detail in Section 8.

Most adverse events will be managed according to standard conventions. General or specific neurologic worsening observed in the first several days after C134 administration could be due to edema, hydrocephalus, hematoma, or encephalitis. Such problems occurring later may also be attributable to tumor progression. When appropriate, an MRI will be done to help determine the cause of the neurologic changes.

- Cerebral edema/hydrocephalus: This commonly occurs in tumor patients post-operatively, and usually responds to standard measures for the treatment of increased intracranial pressure.
- Hematoma: PT, PTT, and platelet count will be obtained. A small hematoma may simply be watched and the patient treated as above for edema and then rescanned to exclude an enlarging lesion. A large hematoma or one associated with progressive neurologic deterioration may require operative evacuation.
- Encephalitis: Post-operative fever is not uncommon. However, fever >102°F (with or without seizures) extending in duration >48 hours, in the presence of a waning Glascow Coma Scale and an increase in the area of hemorrhagic necrosis extending beyond the borders of the tumor on MRI are suggestive of viral encephalitis. If, in the opinion of the PI, it is safe and indicated, a cerebrospinal fluid sample will be obtained and analyzed by polymerase chain reaction (PCR) for evidence of HSV-1. Otherwise, or if CSF results are not diagnostic, a stereotactic biopsy will be considered. This biopsy will be taken to assess for presence of C134 or wild-type HSV-1, as well as for histopathologic evidence of encephalitis. This will consist of a minimum of 2-3 needle core biopsies that will undergo standard hematoxylin and eosin (H&E) staining as well as immunostaining for HSV-1, leucocyte common antigen, and glial fibrillary acidic protein (GFAP) immunostaining. High-dose antiviral therapy with intravenous acyclovir may be implemented in consultation with the Medical Monitor and will be administered according to established method.

5.2 Dosing Delays/Dose Modifications

Because C134 is delivered as a single dose, there will not be any intra-patient dosing delays or dose modifications.

Inter-patient dosing delays and dose modifications are discussed in Section 4.2.

5.3 Study Stopping Criteria

During the trial, if any unexpected Grade 3 or 4 toxicity involving the liver, lungs and heart, or any other Grade 4 toxicity, including grade 5 toxicity, evidence of encephalitis, or disseminated HSV infection (viremia and LFT increase) will be considered stopping criteria. In the event stopping criteria are observed, the trial will be halted until review by the DSMB. The DSMB will make a determination of attribution of the adverse event with the study drug or procedure as well as a decision on whether the trial may proceed.

Adverse events that are expected due to the underlying disease, as outlined in Section 5.1 above, will not trigger stopping of the trial unless the severity is greater than what is expected or if the DSMB determines the event has met stopping criteria. Regardless of attribution to study procedure, study drug, or underlying disease any events of encephalitis/encephalopathy or death will trigger a halt in the trial for review by the DSMB.

6. AGENT FORMULATION AND PROCUREMENT

6.1 C134 Formulation and Storage

cGMP C134 has been produced and certified through the NCI-NeXT program (formerly the Rapid Access to Investigational Drug - Developmental Therapeutics Program RAID-DTP). In brief, It has undergone all of the necessary bio-toxicology, -stability and preclinical safety studies and has received both NCI RAC and FDA IND approval for Phase I study for the treatment of patients with recurrent malignant glioma.

The agent has been prepared at a clinical grade and has met the qualification standards. It was manufactured, filtered, filed and labeled by Leidos Biomedical Research Inc. for Frederick National Laboratory for Cancer Research on November 30, 2011. Stability testing has demonstrated no apparent trend leading to out of specification results at annual time points since that time. Concentration of the virus is 2 x 108 pfu/ml with a limit of > 3 x 10^7 pfu/ml required. It is being stored at -70˚. Clinical material is Lot L1110001, NSC#751997. The virus is tested regularly for appearance, virus titer, expression of HCMV gene IRS1 by western blot, endotoxins/LAL and sterility and has passed all these tests at annual time points.

C134 is supplied in sterile, labeled glass vials that have butyl stoppers crimp sealed containing 0.12 mL of C134 pended in the storage buffer, D-PBS/10% glycerin. The vials should remain frozen at -60°C or below until use.

6.2 C134 Dose Preparation

A single volume of 1.0 mL containing the assigned dose of C134 is prepared for treatment (five inoculations, 0.2 ml each). To prepare the dose, the vial containing C134 should be thawed by removing it from the controlled access -60°C freezer and rubbing the vial gently between gloved hands until the last ice crystals have melted. The vial should then be placed on ice. Care should be taken to ensure that all the liquid is at the bottom of the vial before removing the cap. If it is suspected that the contents are on the side or top of the vial, the vial can be tapped gently on a flat surface. The cap must be removed carefully to avoid spilling or contamination. The appropriate dose level of C134 will be removed from the vial and diluted in sterile saline to the total volume of 1.0 mL. The final diluted C134 should be gently withdrawn into the syringe for injection.

Once thawed and maintained on ice, the dose must be administered to the patient within four hours of preparation.

Complete instructions for dose preparation are described in Appendix B.

6.3 Precautions in Handling C134

Sterile technique and Biosafety Level 2 precautions (gown, gloves, mask) will be rigorously followed while preparing the dose. The dose preparations will take place in a biosafety hood.

6.4 Precautions in Disposal of C134

All materials that have been in contact with C134 are considered infectious biohazards, and must be decontaminated or incinerated prior to disposal. Needles and syringes should be placed into a puncture-resistant, leak-proof container containing disinfectant. All materials that have been in contact with the vector must be incinerated in an institutionally approved biohazard incinerator before disposal.

7. CORRELATIVE/SPECIAL STUDIES

To address secondary objectives of the protocol, additional correlative studies will be performed on blood/serum, conjunctival secretions, saliva samples and tumor tissue samples.

Blood samples will be taken and sera extracted to permit detection and quantification of HSV antibody titer pre-and post-inoculation via ELISA and leukocyte (WBC) subset analysis by FACS. Intracellular lymphocyte interferon γ levels will be assessed by FACS analysis, and lymphocyte transformation assays will also be performed to assess aspects of the T_H1 response to treatment with C134. Conjunctival secretions and saliva will be assessed for HSV shedding.

To determine the tolerability of C134 therapy upon QOL, we will monitor both objective and subjective data on C134 treatment when compared to historical studies using the MD Anderson Symptom inventory –Brain Tumor specific (MDASI-BT; **Appendix C** a validated measure for exploring all aspects of quality of life in patients with malignant glioma. We will compare these results with those provided in a previously published paper that reports these QOL metrics in patients with recurrent malignant brain tumors to determine if there is a trend towards improved QOL with C134 therapy. Similarly, hope versus despair is a major concern for patients with malignant brain tumors, particularly as their disease progresses. We will administer the Hope Herth Index (**Appendix D**) and compare results for patients treated under our study with historic data in the recurrent malignant glioma population that has been previously published (65-68). Both the MDASI-BT and the Hope Herth Index are short and easy to fill-out forms, so patients will not be unduly taxed by having to perform them at follow up visits.

Both subjective (MDASI-BT and the Hope Herth surveys and analysis of burden of treatment) and objective (Karnofsky Performance Status score) will be recorded pre-treatment and then measured serially post-treatment for each patient. Descriptive methods will be used for analysis of questionnaires. Power calculations are not presented for these analyses as the sample size of this Phase I study is unknown.

8. STUDY CALENDAR[13]

	Pre-Study[1]	Day 0[12]	Day 1	Day 2	Day 3	Day 7[2]	Day 10[2]	Day 14[2]	Day 21[2]	Day 28[2]	Month 3[3]	Month 6[3]	Month 12[3]
Informed consent[15]	X[4]												
Demographics	X												
Medical history	X												
Concurrent meds	X	X	X	X	X		X			X	X	X	X
Complete physical exam	X												
Vital signs	X	X[5]	X	X	X		X			X			
KPS	X		X	X	X		X			X	X	X	X
QOL	X									X	X	X	X
CBC w/diff, plts	X			X						X			
Serum chemistry[6], PT/INR, PTT	X			X									
HIV serology	X												
EKG	X												
CXR (AP and lateral)	X												
β-HCG	X[7]												
Urinalysis with micro	X												
Adverse event evaluation		X	X	X	X		X			X	X	X	X
MRI[8]		X[16]			X					X	X	X	X
Neurologic exam	X	X[9]	X	X	X		X			X	X	X	X
HSV Ab titer[10]	X									X	X	X	X
HSV detection (saliva, conjunctival secretions, blood)[11]	X		X[11]	X[11]	X[11]		X[11]			X[11]	X[11]	X[11]	X[11]
Blood sample for LTA, Elispot, WBC subsets	X			X[17]			X			X	X	X	X
Biopsy		X											
C134 Administration		X											
Ophthalmologic evaluation		X[19]				X[18]		X[18]	X[18]				

1. Baseline evaluations are to be conducted within 2 weeks prior to the administration of C134.
2. Acceptable within ±3 days of days 7, 10, 14, and 28.
3. Acceptable within ±12 days of each respective timepoint.
4. Will be obtained prior to study screening procedures.
5. Frequency post-operatively defined by institutional standards and medical need.
6. Includes sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, phosphorus, total protein, uric acid, GGT, AST, CK, LDH, alkaline phosphatase, bilirubin, cholesterol, triglyceride
7. Only women of child-bearing potential
8. All MRI scans will consist of axial fast spin echo, axial flair, axial T1 (pre-gadolinium), and axial T1 (post-gadolinium) sequences. T1 images will be obtained in axial, coronal and sagittal planes. 30 acquisitions will be obtained. T2 weighted images will be obtained in the axial planes only. Review of the baseline MRI scans will be necessary to determine if the tumor location is such that the patient may be included in the study. This baseline study will be obtained a maximum of 30 days prior to the patient's stereotactic inoculation. Unscheduled MRI scans may be done if needed to evaluate post-administration neurological decline.
9. Neurologic function (Glascow Coma Scale and limited neurological function exam) will be evaluated more frequently during the immediate post-operative period as defined by institutional standards and medical need.
10. By ELISA; neutralizing antibody assays may also be performed
11. Samples will be evaluated by PCR and culture; quantitative PCR may be performed on positive samples. Samples will be taken daily until discharge, at day 28 and Months 3, 6 and 12. Close contacts and family members should refrain from direct physical contact until negative shedding data has been recorded.
12. Prior to biopsy and intratumoral inoculation.
13. Appendix E includes the CRFs that will be utilized in this study as a more complete guide to detailed study activities; these are also listed in the Informed consent (ICF).
14. Hope Herth and MDASI-BT will only be conducted pre treatment, , 28, months 3, 6, and 12
15. See Appendix F.
16. If surgeon feels that the biopsy is best done utilizing a technique that requires day of biopsy MRI (e.g., very small target), this will be obtained. If surgeon feels that biopsy is best done using a prior MRI (e.g, using general anesthesia

that requires a specific frame type) a prior MRI will be utilized instead. Catheter placement will be performed according to the method used for biopsy.

17. Acceptable up to Day 4
18. If any HSV Ocular involvement is detected, Acylovir therapy will be immediately initiated.
19. Optional but should not delay treatment

9. MEASUREMENT OF EFFECT

Although response is not the primary endpoint of this trial, patients with measurable disease will be assessed by standard criteria.

9.1 Definitions

Although the Response Evaluation Criteria in Solid Tumors (RECIST) Committee has proposed new international criteria for the evaluation of response and progression of solid tumor, unidimensional measurements alone have not yet been sufficiently validated for the evaluation of malignant gliomas. The iRANO criteria will be used for evaluation of treatment responses (70)

9.1.1 Measurable Disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥10 mm with MRI scan. All intracranial malignant glioma is therefore measurable disease. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

9.1.2 Non-measurable Disease

This type of lesion is not applicable in this study.

9.1.3 Target Lesions

All intracranial lesions that are likely manifestations of the patient's malignancy will be considered target lesions.

9.1.4 Non-target Lesions

This type of lesion is not applicable in this study.

9.2 Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers, or digitized method. All screening evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment. Because all of the patients enrolled in this study will have received prior radiation therapy, tumor lesions that are situated in a previously irradiated area will be considered measurable.
The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is the only means of assessing the antitumor effect of this treatment for this disease.

9.3 Response Criteria

The following criteria are based upon the volume changes that correspond to the definitions proposed by the iRANO criteria (70). For the purposes of this study, the objective response of each patient's disease to C134 will be evaluated by the comparison of a baseline MRI scan to follow-up MRI. For those patients receiving intratumoral inoculation, the screening MRI will serve as the baseline MRI. Response will be evaluated on follow-up scans completed at Day 28, Month 3, Month 6, and Month 12. Additionally, an MRI will be done on Day 3 to evaluate for any early toxicity. To prevent the introduction of observer bias, a software package which determines tumor areas and volumetrics via assessment of pixel intensity will be utilized to compare pre-and post-treatment images.

9.3.1 Evaluation of Target Lesions

"Response" is defined as follows:

Complete Response (CR) - Disappearance of all treated enhancing tumor on MRI scan, off steroids, and neurologically stable or improved.

Partial Response (PR) - greater than 50% reduction in the treated enhancing tumor on MRI scan, stable or reduced steroid dose, and neurologically stable or improved.
Progressive Disease (PD) - greater than 25 % increase in the treated enhancing tumor on MRI scan, stable or increased steroid dose, and neurologically stable or worse.
Stable Disease (SD) - all other situations

Some patients on this trial may be taking dexamethasone and/or bevacizumab. Those who have decreased the dose of one of these medications to one lower than that utilized at the time of the previous MRI AND this dose decrease has occurred within two weeks of the MRI shall not be determined to have progressed even if the MRI meets the criteria for PD above, but rather that MRI shall be considered non-evaluable. Similarly, should an increase in steroid dosage or bevacizumab dosage occur within two weeks of an MRI compared to the prior MRI, the patient will not be eligible for consideration of a CR or PR but instead that MRI will be considered non-evaluable.

Note that since this is considered an immunotherapy trial, the appearance of lesion(s) does not necessarily indicate PD.

9.3.2 Evaluation of Non-target Lesions

Because all intracranial lesions will be considered target lesions, this assessment is not applicable to this study.

9.3.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria (see **section 9.3.1**).

Note: In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is often recommended that the residual lesion be investigated (biopsy) before confirming the complete response status. Because this disease would require a brain biopsy in this situation, with potential increased risk to the patient, patients with an ambiguous complete response status will only undergo histological confirmation if deemed necessary for additional treatment interventions. If tumor is not the predominant feature of biopsy specimen, e.g., if only necrosis is present, or inflammation or gliosis are prominent, then progression will not be deemed to have occurred (Immunotherapy Response Assessment in Neuro-Oncology (iRANO) guidelines(70).

9.3.4 Pseudoprogression

Pseudoprogression is a well-known entity in oncolytic viral therapy of glioma. We will utilize the iRANO criteria to address this phenomenon in this trial: If tumor appears to enlarge or demonstrates increased enhancement by MRI consistent with PD, patients will undergo repeat imaging and clinical assessments at 3 months to determine whether the changes demonstrate true progression or pseudoprogression (70). Note that the investigator may obtain an MRI prior to this 3 month interval as indicated. Should significant neurologic deterioration occur that cannot be ascribed to tumor or pseudoprogression related events such as seizures or medication changes (e.g., steroid tapers) the patient will be considered to have progressed. During the interval, the patient may be watched or treated with bevacizumab and/or dexamethasone at the discretion of the investigators. If the patient improves with bevacizumab (to be used preferentially at a suggested dose of 10mg/kg IV, every two weeks, for three months; previous tumor progression on bevacizumab does not preclude its use herein) and/or additional steroid administration (to be used if bevacizumab is contraindicated or insufficient) and the MRI changes in lesion size/and or enhancement also improves, the patient will be determined to have not progressed but to have suffered pseudoprogression, and will continue follow-up within the trial under the previously defined schedule. Should neurologic symptoms and/or imaging changes progress despite steroid administration on follow-up imaging, the patient will be determined to have progressed and the date

of progression shall be assigned to the date of the initial scan that demonstrated findings consistent with PD as defined above.

9.4 Confirmatory Measurement/Duration of Response

9.4.1 Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by the next scheduled MRI after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 12 weeks.

9.4.2 Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

9.4.3 Duration of Stable Disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

9.5 Progression-Free Survival

Because this study is a non-randomized phase 1 trial that will enroll relatively few patients, progression-free survival will be reported as a secondary endpoint.

10. REGULATORY AND REPORTING REQUIREMENTS

10.1 Expedited Adverse Event Reporting

Adverse events (AE) will use the descriptions and grading scales found in the revised NCI Common Toxicity Criteria (CTC). This study will utilize the CTCAE 4.0 for adverse event reporting. All appropriate treatment areas will have access to a copy of the CTCAE 4.0. A table showing the expected adverse events associated with the underlying disease of the subjects can be found in Section 5.1.

Expedited Adverse Event Reporting (AE; formerly known as Adverse Drug Reaction)

10.1.1 Expedited Reporting Guidelines – Phase 1 studies with investigational agents:

UNEXPECTED EVENT		EXPECTED EVENT	
GRADES 2 – 3 **Attribution of Possible, Probable or Definite**	**GRADES 4 and 5** **Regardless of Attribution**	**GRADES 1 - 3**	**GRADES 4 and 5** **Regardless of Attribution**
Grade 2 - Expedited report within 10 working days. **Grade 3** - Report by phone to IDB within 24 hrs. Expedited report to follow within 10 working days. (**Grade 1** – Adverse Event Expedited Reporting NOT required.)	Report by phone to IDB within 24 hrs. Expedited report to follow within 10 working days. This includes deaths within 30 days of the last dose of treatment with an investigational agent.	Adverse Event Expedited Reporting NOT required.	Report by phone to IDB within 24 hrs. Expedited report to follow within 10 working days. This includes deaths within 30 days of the last dose of treatment with an investigational agent.

- For grade 2-3 unexpected events, the investigator will be unbiased in assessing the relationship of the event and test article and discuss the possible relatedness to treatment with the Medical Monitor.
- Adverse event and IND safety reports will be filed in a timely manner with institutional authorities (IRB, IBC) as well as with the FDA and NIH/ORDA
- All serious adverse events (Grade 3 or 4 toxicities will be reported by fax, e-mail or phone within 24 hours and a written expedited report filed within ten days. Additionally, unexpected Grade 2 or Grade 3 toxicities will require a written expedited report within ten days and Grade 3 unexpected adverse events will also require a fax, email, or phone call to the the UAB IRB, the UAB CCC DSMP, FDA, and OBA within 24 hours.
- A list of disease-specific expected adverse events can be found in Section 5.1.
- Any adverse event requiring an expedited report will also be reported immediately to the Medical Monitor and the investigator's Institutional Review Board (IRB).
- Patients administered C134 will be subject to long term follow-up (15 years) to detect potential delayed adverse events.

10.1.2 Forms

1. Although C134 will not be obtained from the NCI, the standard DCTD Form for Reporting AEs Occurring with Investigational Agents will still be used. This form can be downloaded from the CTEP home page (https://ctep.cancer.gov/forms/docs/34-adeers_v3-0_sat_11-21-00.pdf).

10.1.3 Secondary Malignancies

Investigators are required to report secondary malignancies occurring on or following treatment on NCI-sponsored protocols using the form noted above. **Exception**: Cases of secondary AML/MDS are to be reported using the NCI/CTEP Secondary AML/MDS Report Form.

10.2 Data Reporting

This study will be conducted under the oversight of the UAB Comprehensive Cancer Center for which a Data and Safety Monitoring Plan has been established.

10.3 CTEP Multicenter Guidelines: N/A

10.4 Cooperative Research and Development Agreement (CRADA)/Clinical Trials Agreement (CTA): N/A

10.5 Study Monitoring:

CTNMO will be responsible for the monitoring of study patient data and records.
All monitoring reports will be kept by the UAB CTNMO to ensure that all reports are contained in a central study file. A final monitoring report will be generated and issued to the site and will be kept in the central study file by the UAB CTNMO. The staff of the UAB CTNMO will notify the participating site of any data queries and manage the overall data quality of the study.
All data will be substantiated by clinical source documents organized within a patient research record. ICH Good Clinical Practices are to be followed.

The study will be subject to a yearly internal audit via the UAB CCC Quality Assurance Committee at a minimum and audits may occur more frequently at the request of the QA Committee.

11. STATISTICAL CONSIDERATIONS

11.1 Study Design/Endpoints

This study is an open-label, dose escalating phase 1 study of the safety of intracranial administration of C134, an IRS1-chimeric HSV1, a genetically engineered HSV-1 expressing CMV IRS1. For this reason, the primary endpoint of this study is to determine the safety and tolerability of a single stereotactic intracerebral injection of escalating doses of C134 virus, and to determine the maximally tolerated dose (MTD). The dose escalation scheme and the definition of the MTD are found in Section 4.1. Because C134 is administered as a single dose intrapatient dose escalations will not be feasible.

Demographic Analysis: Demographic and baseline characteristics will be summarized for each cohort using the statistics of number, mean, median and range for continuous variables and for discrete factors, values will be tabulated.

Safety Analysis: Descriptive statistics will be used in the reporting of adverse events. Adverse events will be tabulated and frequencies of events will be determined. All events with a toxicity of Grade 3 or above will be tabulated by event, as well as tabulations for all events (where toxicity is defined by the Common Toxicity Criteria). Laboratory analyses (chemistries, hematology, urinalysis, serological/immunological analyses, WBC and differential) will consist of measurements of change from baseline over time by patient and overall, with plots of actual values compared to normal values for patients by dose group. Logarithmic transformations may be applied as necessary. Group means and standard errors will be calculated for the various laboratory parameters. Concurrent Illnesses will be listed and examined by univariate and multivariable analysis as possible confounders in the treatment response relationship. Concurrent medications will also be listed. Effects of previous treatments for cancer will also be examined by univariate and multivariable analysis, and any potential related side effects will be analyzed and discussed.

11.2 Sample Size/Accrual Rate

Because the number of patients enrolled at each dose level depends on observed toxicities, it is not possible to state a definite sample size that will be accrued. The dose escalation plan does allow for a minimum of 2 4 patients to be enrolled (if the first two patients enrolled experienced dose-limiting toxicity, then 2 dose de-escalations occur with a single patient enrolled at each level) and a maximum of 24 patients to be enrolled. It is expected that the actual enrollment will fall well between these two extremes. It is expected that this study will accrue approximately 10 patients per year.

11.3 Stratification Factors

This study will not stratify patients according to any baseline factors.

11.4 Analysis of Secondary Endpoints

11.4.1 Characterization of the in situ activity of C134 after intratumoral inoculation.

- Durability and replication of C134 in the resected tumor will be evaluated by the presence or absence of HSV DNA and RNA.
- *In situ* ability of C134 to induce an inflammatory T_{H1}-type response will be assessed by ELISA for interferon-γ.
- Each of these binomial responses will be summarized by frequencies for each cohort and overall.

11.4.2 Delineation of the local and systemic immune response to C134 administration.

- Virus reactivation and shedding will be detected by PCR and culture of serial serum and saliva samples.
- Immunogenecity of C134 will be evaluated by the use of ELISA to detect HSV antibody titers in serial serum samples.
- Local inflammatory infiltrate at the site of C134 intratumoral inoculation will be characterized by use of immunohistochemistry when possible and systemic response evaluated by leukocyte subset analysis via FACS analysis.
- Each of these binomial responses will be summarized by frequencies for each cohort and overall.

11.4.3 Gather preliminary information about the potential benefit of C134 in the treatment of patients with recurrent malignant gliomas.

- The percentage of patients experiencing complete response, partial response, stable disease and progressive disease will be reported by cohort and overall based on follow-up radiographic imaging.
- Changes in clinical disease status and steroid administration will be considered when reviewing changes in tumor volumetric size.
- All changes in tumor volume will also be analyzed with consideration of any other anti-tumor cancer therapies (either prior to C134 administration or following C134 failure) and the timeframes in which they were administered.
- Quality of life response: A Karnofsky Performance Status (KPS) score will be recorded pre-treatment and then measured serially post-treatment for each patient. Time to KPS <60 will be measured for each patient by the Kaplan-Meier analytical method.

11.4.4 Remnant tumor specimens' studies

- Remnant tumor specimens from the trial will be studied for evidence of C134 and antitumor responses via molecular testing. Such tests will include RNAseq, Nanostring, Spatial transcriptomic analysis, nucleic acid analyses, proteinomics and other protein analyses, cytokine and chemokine analyses

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ABBREVIATIONS USED:

Chimeric Virus (short form “chimeric”): A genetically-engineered virus with one or more genes from at least two different parent viruses

CMV, HCMV: Human Cytomegalovirus

DLT: Dose Limiting Toxicity

G207-oHSV initially studied in the U.S. in patients with recurrent malignant glioma that is a $\Delta\gamma_1$34.5 but also has another deletion in the viral ribonucleotide reductase gene that renders the virus markedly debilitated.

GBM: Glioblastoma multiforme

HSV: Herpes Simplex Virus Type 1

oHSV: oncolytic Herpes Simplex Virus Type 1

$\gamma_1$34.5: HSV1 gene responsible for neurovirulence, shutdown of host protein synthesis, and other functions.

$\Delta\gamma_1$34.5 HSV or HSV-1: Viruses deleted for the $\gamma_1$34.5 gene

IRS-1: A CMV gene that is responsible for antagonizing protein kinase R (PKR) to increase the replication of CMV. IRS-1 is closely related to TRS-1

PKR: Protein Kinase R, a protein expressed by cells involved in innate cellular resistance to viral infection. When a DNA virus infects the cell, PKR acts to interfere with viral replication within the cell.

TRS-1: A CMV gene that is responsible for antagonizing protein kinase R (PKR) to increase the replication of CMV. TRS-1 is closely related to IRS-1

APPENDIX:

APPENDIX A

C134	Month 3 (± 12 days)	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

KARNOFSKY PERFORMANCE SCALE	
Percent	***Description***
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 to do active work.
60	Requires occasional assistance, but is able to care for most of his/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.
0	Dead.

Karnofsky Performance Scale: _____%

COMPLETE NEUROLOGICAL EXAM		
Level of Consciousness:	☐ Alert ☐Sleepy, but easily aroused ☐Somnolent/difficult to arouse ☐Not arousable	
Orientation:	Oriented to time: ☐Yes ☐ No Oriented to place: ☐Yes ☐ No Oriented to self, person and others: ☐Yes ☐ No	
Muscle Strength: (enter corresponding number)	0 = None 1 = Trace 2 = Gravity eliminated 3 = Against gravity 4 = Against resistance 5 = Normal	Right Arm: _____ Right Leg: _____ Left Arm: _____ Left Leg: _____
Gait Evaluation:	☐ Normal ☐ Mildly ataxic ☐ Requires a cane ☐Non-ambulatory ☐Unable to evaluate	
Cranial Nerves: Are any cranial nerves affected?	☐ Yes	Left: II III IV V VI VII VIII IX X XI XII Right: II III IV V VI VII VIII IX X XI XII ☐ No
Sensory Exam: Are there abnormalities present? (performed as relevant to tumor location/signs/ symptoms)	☐ Yes_____ ☐ No	
Other Neurological Findings:		
Comments:		

Appendix B Table: Dose Preparation Guide

Dose Range 1x10e6 - 1x10e8

Total Infusion Volume: 1 ml

	Concentration (PFU/ml)	Vol (ml)	Virus (PFU)
C134 Samples	3.13E+08	0.3	93900000

Desired Dose and Concentration

For <1x10e7 samples prepare a diluted sample of C134 (5x10e7/ml) in the glass vial containing the stock virus

Target conc	Starting virus	Volume of virus	Diluent (ml)	Final Conc C134
5.00E+07	3.13E+08	0.3	1.6	4.94E+07

Dose (PFU)	**Concentration (PFU/ml)**	***Diluted Virus (4.94x10e7 PFU/ml)**	**Diluent (ml)**	**Concentration (PFU/ml**
1.00E+06	1.00E+06	0.2	9.6	1.01E+06
3.33E+06	3.33E+06	0.6	8.2	3.37E+06
1.00E+07	1.00E+07	1	3.8	1.03E+07
3.33E+07	3.33E+07	2	1	3.29E+07

Dose (PFU)	**Concentration (PFU/ml)**	**Stock Virus (3.18e8 PFU/ml)**	**Diluent (ml)**	**Concentration (PFU/ml)**
Target conc		Present in bottle	Add to bottle	Final Conc C134
1.00E+08	1.00E+08	0.3	0.7	9.39E+07

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

Study Name: _____

Protocol #: _____

PI: _____

Subject Initials: ☐☐☐

MD Anderson # : ☐☐☐☐☐☐

PDMS # : ☐☐☐☐

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

Part I. How severe are your symptoms?

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

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

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

Study Name: _____

Protocol #: _____

PI: _____

Subject Initials: _____

MD Anderson # : ☐☐☐☐☐☐ PDMS # : ☐☐☐☐

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

Part II. How have your symptoms interfered with [illegible]

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

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

Well-being

Hope

Herth Hope Index

 Study No._____

HERTH HOPE SCALE

Listed below are a number of statements regarding hope. Read each statement and decide whether it applies to you personally. There are no right or wrong answers. Place a check [X] in the appropriate box indicating how often the statement has applied to you in the past week or two.

	Never applies to me	Seldom applies to me	Sometimes applies to me	Often applies to me
1. I am looking forward to the future.				
2. I sense the presence of loved ones.				
3. I have deep inner strength.				
4. I have plans for the future.				
5. I have inner positive energy.				
6. I feel scared about my future.				
7. I keep going even when I hurt.				
8. I have a faith that gives me comfort.				
9. I believe that good is always possible.				
10. I feel at a loss, no where to turn.				
11. I feel time heals.				
12. I have support from those close to me.				
13. I feel overwhelmed and trapped.				
14. I can recall happy times.				

15. I just know there is hope.				
16. I can seek and receive help.				
17. I am immobilized by fears and doubts.				
18. I know my life has meaning and purpose.				
19. I see the positive in most situations.				
20. I have goals for the next 3-6 months.				
21. I am committed to finding my way.				
22. I feel all alone.				
23. I have coped well in the past.				
24. I feel loved and needed.				
25. I believe that each day has potential.				
26. I can't bring about positive change.				
27. I can see a light even in a tunnel.				
28. I have hope even when plans go astray.				
29. I believe my outlook affects my life.				
30. I have plans for today and next week.				

HERTH HOPE SCALE

HERTH HOPE INDEX				
Listed below are a number of statements. Read each statement and place an [X] in the box that describes how much you agree with that statement right now.				
	Strongly Disagree	**Disagree**	**Agree**	**Strongly Agree**
1. I have a positive outlook toward life.				
2. I have short and/or long range goals.				
3. I feel all alone.				
4. I can see possibilities in the midst of difficulties.				
5. I have a faith that gives me comfort.				
6. I feel scared about my future.				
7. I can recall happy/joyful times.				
8. I have deep inner strength.				
9. I am able to give and receive caring/love.				
10. I have a sense of direction.				
11. I believe that each day has potential.				
12. I feel my life has value and worth.				

SCORING INFORMATION FOR THE HERTH HOPE SCALE (HHS)

Scoring consists of summing the ratings for the subscales and for the total scale. Subscales are based on the three factors (see Table 2 in 1991 publication). Total possible points on the total scale is 90 points. The higher the score the higher the level of hope.

Note the following items need to be reversed scored: 6, 10, 13, 17, 22, 26. Score items as follows:

Never applies to me = 0
Seldom applies to me = 1
Sometimes applies to me = 2
Often applies to me = 3

HHS has been translated into Chinese, Spanish, Swedish, Tai, Norwegian and German.

Herth, K. (1991). Development and refinement of an instrument to measure hope. Scholarly Inquiry for Nursing Practice: An International Journal, 5(1), 39-51.

SCORING INFORMATION FOR THE HERTH HOPE INDEX (HHI)

Scoring consists of summing the points for the subscale and for the total scale. Subscales are based on the three factors (see Table 2 in 1992 publication). Total possible points on the total scale is 48 points. The higher the score the higher the level of hope.

Note the following items need to be reversed scored: 3, 6. Score items as follows:

Strongly Disagree = 1
Disagree = 2
Agree = 3
Strongly Agree = 4

HHI has been translated into Swedish, Japanese, Norwegian, Spanish and German.

Herth, K. (1992). Abbreviated instrument to measure hope: Development and psychometric evaluation. Journal of Advanced Nursing, 17, 1251-1259.

CASE REPORT FORM

A Phase I Trial of IRS-1 HSV C134 Administered Intratumorally in Patients with Recurrent Malignant Glioma

CLINICAL TRIAL SITE: **UAB**

PRINCIPAL INVESTIGATOR: **James M. Markert, MD**

Subject Initials: ___ ___ ___

Subject Number: ___ ___ ___

Enrollment Date: ___ ___ ___

I am confident that the information supplied in this case record form is complete and accurate data. I confirm that the study was conducted in accordance with the protocol and any protocol amendments and that written informed consent was obtained prior to the study.

Investigator's Signature: _____

Date of signature: _____ _____ _____
dd mmm yyyy

C134	Pre-Study (Enrollment Visit) Date: ____ ____ ____ dd mmm yyyy	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

INCLUSION CRITERIA			
		Yes	**No***
1	Does the subject have histologically or cytologically confirmed *glioblastoma multiforme*, anaplastic astrocytoma, or gliosarcoma?	☐	☐
2	Has the subject failed external beam radiotherapy ≥5,000 cGy to the brain, and if eligible and tolerated, undergone appropriate treatment with temozolomide chemotherapy? *(All radiation and additional chemotherapies must have been completed at least 4 weeks prior to enrollment. Prior therapy with nitrosoureas must have been completed at least 6 weeks prior to enrollment.)*	☐	☐
3	Is subject's age ≥19 years?	☐	☐
4	Is subject's Karnofsky Performance Status ≥70%?	☐	☐
5	Is subject's life expectancy greater than 4 weeks?	☐	☐
6	Does subject have normal organ and marrow function as defined below: • leukocytes……...≥3,000/µl • absolute neutrophil count……..≥1,500/µl • platelets……...≥100,000/µl • total bilirubin…….within normal institutional limits • AST(SGOT)/ALT(SGPT)……..≤2.5 X institutional upper limit of normal • creatinine…….within normal institutional limits OR creatinine clearance……...≥60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.	☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐
7	Is subject's residual lesion ≥1.0 cm in diameter as determined by MRI?	☐	☐
8	Does subject (women of child-bearing potential and men) agree to use adequate contraception (barrier method) prior to study entry and for the first six months after receiving C134, to avoid intimate contact with pregnant women, infants and young children and individuals with decreased immunity (ability to fight infection) for two weeks after receiving C134, and to refrain from donating blood during the trial?	☐	☐
9	Does subject have the ability to understand and the willingness to sign a written informed consent document?	☐	☐
10	Females of childbearing potential must not be pregnant: Has this been confirmed by negative serum pregnancy test within 14 days prior to starting study treatment?	☐	☐

***If any inclusion criteria are checked "No" then the patient is not eligible for the study.**

C134	Pre-Study (Enrollment Visit) Date: ____ ____ ____ dd mmm yyyy	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

EXCLUSION CRITERIA		
	Yes*	***No***
1. Has subject had chemotherapy, cytotoxic therapy, immunotherapy within 4 weeks prior to entering the study (6 weeks for nitrosoureas), surgical resection within 4 weeks prior to entering the study, or have received experimental viral therapy or gene therapy at any time (e.g., adenovirus, retrovirus or herpes virus protocol)? (*However, this does not preclude re-treatment with C134 at a later date.)*	☐	☐
2. Has subject not recovered from adverse events due to therapeutic interventions administered more than 4 weeks earlier?		
3. Is subject receiving any other investigational agents?	☐	☐
4. Does subject have a history of allergic reactions attributed to compounds of similar biologic composition to C134?	☐	☐
5. Does subject have tumor involvement which would require ventricular, brainstem, basal ganglia, or posterior fossa inoculation or would require access through a ventricle in order to deliver treatment?	☐	☐
6. Does subject have a prior history of encephalitis, multiple sclerosis, or other CNS infection?	☐	☐
7. Has subject required steroid increase within 2 weeks of scheduled C134 administration?	☐	☐
8. Does subject have any active herpes lesions?	☐	☐
9. Is subject receiving concurrent therapy with any drug active against HSV (acyclovir, valacyclovir, penciclovir, famcyclovir, gancyclovir, foscarnet, cidofovir)?	☐	☐
10. Does subject have any uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, any other medical condition that precludes surgery or psychiatric illness/social situations that would limit compliance with study requirements?	☐	☐
11. Is Subject: • A pregnant woman (excluded from this study because C134 is a viral oncolytic therapy with unknown potential for teratogenic or abortifacient effects)? • Breastfeeding (there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with C134)? • Immune deficient (will be unable to mount the anticipated immune response underlying this therapeutic rationale, HIV-seropositive patients are excluded from this study)?	☐ ☐ ☐	☐ ☐ ☐
12. Does subject have a known history of allergic reaction to IV contrast material that is not amenable to pre-treatment by UAB protocol?	☐	☐
13. Does subject have a pacemaker, ferro-magnetic aneurysm clips, metal infusion pumps, metal or shrapnel fragments, or certain types of stents?	☐	☐
14 Has subject received Gliadel Therapy?	☐	☐
15. Has subject received Bevacizumab (Avastin) therapy within 4 weeks of scheduled C134 administration? (Receipt of Bevacizumab (Avastin) greater than 4 weeks of scheduled C134 administration does not exclude patient.)	☐	☐
**** If any exclusion criteria are checked "Yes" then the patient is not eligible for the study.***		

C134	Pre-Study (Enrollment Visit) Date: ____ ____ ____ dd mmm yyyy	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

INFORMED CONSENT		
Does subject meet all inclusion/exclusion criteria?	☐ Yes	☐ No
Has the subject freely given written informed consent?	☐ Yes	☐ No
Date signed (ddmmmyyy): _____	Time (24 hour clock): _____	

DEMOGRAPHICS		
Age (yrs.): _____	Date of Birth (ddmmmyyyy): _____	
Gender: ☐ Female ☐ Male	Race: ☐ Black ☐White ☐Asian ☐Other Ethnicity: Hispanic ☐Yes ☐ No	

PREVIOUS MEDICAL HISTORY

Is there any relevant medical history in the following systems?

System	*Yes*	*No*	*Comments*	*Onset Date* (ddmmmyyy)	*Ongoing*
Cardiovascular	☐	☐			☐ Yes ☐ No
Respiratory	☐	☐			☐ Yes ☐ No
Hepatobiliary	☐	☐			☐ Yes ☐ No
Gastrointestinal	☐	☐			☐ Yes ☐ No
Genitourinary	☐	☐			☐ Yes ☐ No
Endocrine	☐	☐			☐ Yes ☐ No
Hematological	☐	☐			☐ Yes ☐ No
Musculoskeletal	☐	☐			☐ Yes ☐ No
Neurological	☐	☐			☐ Yes ☐ No
Psychological	☐	☐			☐ Yes ☐ No
Immunological	☐	☐			☐ Yes ☐ No
Dermatological	☐	☐			☐ Yes ☐ No
Allergies	☐	☐			☐ Yes ☐ No
HEENT	☐	☐			☐ Yes ☐ No
Other _____	☐	☐			☐ Yes ☐ No

C134	Pre-Study (Enrollment Visit) Date: ____ ____ ____ dd mmm yyyy	Subject Initials: __ __ __	Subject Number: __ __ __

MEDICATIONS		
Is the subject currently or previously taking any medications including prescription, OTC, vitamins and/or supplements?	☐ Yes	☐ No
Record all medication on Concomitant Medications CRF		

VITAL SIGNS	
Height (cm): _____._____	Weight (kg): _____._____
Blood Pressure: _____/_____	Heart Rate: _____ bpm
Respiratory Rate: _____	Temperature: _____._____ °C

PHYSICAL EXAMINATION				
System	***Normal***	***Abnormal***	***Not Done***	***Describe if abnormal or give reason not completed***
General Appearance	☐	☐	☐	
HEENT	☐	☐	☐	
Cardiovascular	☐	☐	☐	
Pulmonary	☐	☐	☐	
Abdomen	☐	☐	☐	
Musculoskeletal	☐	☐	☐	
Extremities	☐	☐	☐	
Lymph Nodes	☐	☐	☐	
Dermatology	☐	☐	☐	
Other, Specify _____	☐	☐	☐	
Other, Specify _____	☐	☐	☐	

C134	Pre-Study (Enrollment Visit) Date: ____ ____ ____ dd mmm yyyy	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

COMPLETE NEUROLOGICAL EXAM

Level of Consciousness: ☐ Alert ☐Sleepy, but easily aroused ☐Somnolent/difficult to arouse ☐Not arousable

Orientation:
Oriented to time: ☐Yes ☐ No
Oriented to place: ☐Yes ☐ No
Oriented to self, person and others: ☐Yes ☐ No

Muscle Strength: (enter corresponding number)
0 = None
1 = Trace
2 = Gravity eliminated
3 = Against gravity
4 = Against resistance
5 = Normal

Right Arm: _____ Right Leg: _____
Left Arm: _____ Left Leg: _____

Gait Evaluation: ☐ Normal ☐ Mildly ataxic ☐ Requires a cane ☐Non-ambulatory ☐Unable to evaluate

Cranial Nerves:
Are any cranial nerves affected? ☐ Yes ☐ No
Left: II III IV V VI VII VIII IX X XI XII
Right: II III IV V VI VII VIII IX X XI XII

Sensory Exam:
Are there abnormalities present?
(performed as relevant to tumor location/signs/ symptoms)
☐ Yes_____
☐ No

Other Neurological Findings:

Comments:

KARNOFSKY PERFORMANCE SCALE

Percent	*Description*
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 to do active work.
60	Requires occasional assistance, but is able to care for most of his/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.
0	Dead.

Karnofsky Performance Scale: _____**%**

PREGNANCY STATUS

Date of procedure (ddmmmyyyy): _____
Pregnancy test-serum ☐ Positive** ☐ Negative ☐ NA

Unable to participate in this study

C134	Pre-Study (Enrollment Visit) Date: ____ ____ ____ dd mmm yyyy	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

CHEST X-RAY (AP and Lateral)

Date of procedure (dd/mmm/yyyy) : _____

Is the X-ray: ☐ Normal ☐ Abnormal **

**Description: _____

EKG

Date of procedure (ddmmmyyyy) : _____

Is the EKG: ☐ Normal ☐ Abnormal **

**Description: _____

MRI

Date of procedure (ddmmmyyyy): _____

Does the MRI meet eligibility requirements (≥ 1 cm): ☐ Yes ☐No

Measurement: _____ cm

LABORATORY ANALYSIS

CBC with diff, plts **Date drawn** (ddmmmyyyy): _____

Test	*Results*		*Clinically Significant*
• Red blood cell count (RBC) o M: 4.40 – 5.80 x 10^6/cmm o F: 3.80 – 5.20 x 10^6/cmm	_____ x 10^6/cmm	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Hemoglobin (Hgb) o M: 13.5 – 17.0 g/dL o F: 11.3 – 15.2 g/dL	_____ g/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Hematocrit (Hct) o M: 39 – 50% o F: 33 – 45%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Platelet count (PLT) o 150- 400 x 10^3/cmm	_____ x 10^3/cmm	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• White blood cell count (WBC) o 4.0 – 11.0 x 10^3/cmm	_____ x 10^3/cmm	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Neutrophils • 35 – 73%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Lymphocytes o 15 – 52%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No

C134	Pre-Study (Enrollment Visit) Date: ____ ____ ____ dd mmm yyyy	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

LABORATORY ANALYSIS **CBC with diff, plts (cont.)**			
Test	***Results***		***Clinically Significant***
▪ Monocytes o 4 – 13%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Basophils o 0 – 2%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Eosinophils o 0 – 5%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Mean corpuscular haemoglobin (MCH) o 27 – 33 pg	_____ pg	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Mean corpuscular haemoglobin concentration (MCHC) o 32 – 36 g/dL	_____ g/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Mean corpuscular volume (MCV) o 80 – 96 fL	_____ fL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No

LABORATORY ANALYSIS **Serum Chemistry** **Date drawn** (ddmmmyyyy)**:** _____			
Test	***Results***		***Clinically Significant***
• Sodium (Na) o 133 – 145 mEq/L	_____ mEq/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Potassium (K) o 3.1 – 5.1 mEq/L	_____ mEq/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Chloride (Cl) o 97 – 108 mEq/L	_____ mEq/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Bicarbonate (CO_2) o 22 – 32 mEq/L	_____ mEq/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Glucose o 70 – 100 mg/dL (fasting) o 70 – 200 mg/dL (non-fasting)	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Blood urea nitrogen (BUN) o 5 – 22 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No

LABORATORY ANALYSIS

Serum Chemistry (cont.)

Test	*Results*		*Clinically Significant*
• Creatinine o M: 0.7 – 1.3 mg/dL o F: 0.4 – 1.2 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Calcium (Ca) o 8.4 – 10.2 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Phosphorus o 2.4 – 5.0 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Total protein o 6.0 – 8.3 g/dL	_____ g/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Uric acid o M: 3.9 – 8.1 mg/dL o F: 2.0 – 6.9 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Gamma-glutamyl transferase (GGT) o 0 – 65 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Aspartate aminotransferase (AST) o 12 – 39 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Alanine aminotransferase (ALT) o 7 - 52 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Creatine kinase (CK) o M: 35 – 250 Units/L o F: 25 – 190 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Lactate dehydrogenase (LDH) o 120 – 240 Units/L	_____ IU/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Alkaline phosphatase (Alk Phos) o 39 – 117 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Total bilirubin o 0.3 – 1.4 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Cholesterol (Chol) o 100 – 200 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Triglycerides (TG) o 40 – 150 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No

LABORATORY ANALYSIS

Serum Chemistry (cont.)

Test	*Results*		*Clinically Significant*
• Prothrombin time/INR (PT/INR) o 12.0 - 14.5 seconds	_____ seconds	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Partial thromboplastin time (PTT) o 25.0 – 35.0 seconds	_____ seconds	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Human Immunodeficiency virus type 1&2 (HIV 1 / 2 antibody) o Negative	☐ Negative ☐ Positive	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No

Retain signed and dated report in the plastic sleeve at back of CRF Folder

LABORATORY ANALYSIS

Urinalysis **Date collected** (ddmmmyyyy): _____

Test	*Results*		*Clinically Significant*
• Color o Yellow, Straw, Amber	_____	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Clarity o Clear	_____	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Specific Gravity o 1.003 – 1.035	_____	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• pH o 4.6 – 8.0		☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Protein o Negative	☐ Negative ☐ Positive	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Glucose o Negative	☐ Negative ☐ Positive	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Ketones o Negative	☐ Negative ☐ Positive	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Blood o Negative	☐ Negative ☐ Positive	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Nitrite o Negative	☐ Negative ☐ Positive	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No

C134	Pre-Study (Enrollment Visit) Date: ____ ____ ____ dd mmm yyyy	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

LABORATORY ANALYSIS **Urinalysis (cont.)**			
Test	***Results***		***Clinically Significant***
• Leukocyte estimate o Negative	☐ Negative ☐ Positive	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Bilirubin o Negative	☐ Negative ☐ Positive	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Urobilinogen o Negative	☐ Negative ☐ Positive	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
If Dipstick Analysis is clinically significant, please perform the following microscopic exam			**☐ NA**
• White blood cells (WBC) o 0 – 5 hpf	_____ hpf	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Red blood cells (RBC) o 0 – 2 hpf	_____ hpf	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Squamous epithelial cells o Negative	☐ Negative ☐ Positive	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Non-squamous epithelial cells o Negative	☐ Negative ☐ Positive	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Yeast o Negative	☐ Negative ☐ Positive	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Amorphous cells o Negative	☐ Negative ☐ Positive	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Mucous in urine o Negative	☐ Negative ☐ Positive	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Casts o Negative	☐ Negative ☐ Positive	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Crystals o Negative	☐ Negative ☐ Positive	☐ Normal ☐ Not done	☐ Yes ☐ No

C134	Pre-Study (Enrollment Visit) Date: ____ ____ ____ dd mmm yyyy	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

LABORATORY ANALYSIS						
HSV Detection		**Date collected** (ddmmmyyyy)**:** _____				
Test	***Results***					***Clinically Significant***
Saliva	☐ Negative	☐ Positive	☐ Normal	☐ Abnormal	☐ Not done	☐ Yes ☐ No
Conjunctival	☐ Negative	☐ Positive	☐ Normal	☐ Abnormal	☐ Not done	☐ Yes ☐ No
Blood	☐ Negative	☐ Positive	☐ Normal	☐ Abnormal	☐ Not done	☐ Yes ☐ No

RESEARCH SAMPLES			
Date drawn (ddmmmyyyy): _____			
Test	***Yes***	***No***	***Comments***
HSV Antibody Titer	☐	☐	
LTA, Elispot-blood	☐	☐	
IFN Gamma Assay	☐	☐	
Blood for future research	☐	☐	

DAY 0 **Date:** _____
ddmmmyyyy

VITAL SIGNS (Pre-surgery)	
Weight (kg): _____._____	
Blood Pressure: _____/_____	Heart Rate: _____ bpm
Respiratory Rate: _____	Temperature: _____._____°C

COMPLETE NEUROLOGICAL EXAM		
Level of Consciousness:	☐ Alert ☐Sleepy, but easily aroused ☐Somnolent/difficult to arouse ☐Not arousable	
Orientation:	Oriented to time: ☐Yes ☐ No Oriented to place: ☐Yes ☐ No Oriented to self, person and others: ☐Yes ☐ No	
Muscle Strength: (enter corresponding number)	0 = None 1 = Trace 2 = Gravity eliminated 3 = Against gravity 4 = Against resistance 5 = Normal	Right Arm: _____ Right Leg: _____ Left Arm: _____ Left Leg: _____
Gait Evaluation:	☐ Normal ☐ Mildly ataxic ☐ Requires a cane ☐Non-ambulatory ☐Unable to evaluate	
Cranial Nerves: Are any cranial nerves affected?	☐ Yes	Left: II III IV V VI VII VIII IX X XI XII Right: II III IV V VI VII VIII IX X XI XII ☐ No
Sensory Exam: Are there abnormalities present? (performed as relevant to tumor location/signs/ symptoms)	☐ Yes_____ ☐ No	
Other Neurological Findings:		
Comments:		

ADVERSE EVENTS	
Has the subject experienced any adverse events since last visit?	☐Yes ☐ No
Record all Adverse Events on Adverse Events CRF	

MEDICATIONS	
Have there been any changes to medications?	☐ Yes ☐ No
Record all medications on Concomitant Medications CRF	

DAY 0 (cont.)

MRI
Was Stereotactic MRI completed? ☐ Yes ☐No Why?:_____

PRELIMINARY PATHOLOGY REPORT		
Biopsy confirms diagnosis of recurrent/progressive glioblastoma, anaplastic astrocytoma or gliosarcoma	☐ Yes	☐No

CATHETERS
Number of catheters placed: _____

RESEARCH SAMPLES			
Date drawn: _____ dd/mmm/yyyy			
Test	***Yes***	***No***	***Comments***
Blood for future research – post-op	☐	☐	

DAY 1 **Date:** _____
ddmmmyyyy

CT			
Was CT completed prior to study drug administration?	☐ Yes	☐No	Comment:_____
Date completed (dd/mmm/yyyy): _____			
Are all catheters in proper position?	☐ Yes	☐No	Comment:_____

ADVERSE EVENTS		
Has the subject experienced any adverse events since last visit?	☐Yes	☐ No
Record all Adverse Events on Adverse Events CRF		

MEDICATIONS		
Have there been any changes to medications?	☐ Yes	☐ No
Record all medication on Concomitant Medications CRF		

PHYSICAL EXAMINATION

System	*Normal*	*Abnormal*	*Not Done*	*Describe if abnormal or give reason not completed*
General Appearance	☐	☐	☐	
HEENT	☐	☐	☐	
Cardiovascular	☐	☐	☐	
Pulmonary	☐	☐	☐	
Abdomen	☐	☐	☐	
Musculoskeletal	☐	☐	☐	
Extremities	☐	☐	☐	
Lymph Nodes	☐	☐	☐	
Dermatology	☐	☐	☐	
Wound Assessment	☐	☐	☐	
Other, Specify _____	☐	☐	☐	

VITAL SIGNS
See Vital Signs CRF for Days 1-3

COMPLETE NEUROLOGICAL EXAM
See Neurological Exam CRF for Days 1-3

STUDY DRUG ADMINISTRATION
See Catheter CRF

DAY 2 **Date:** _____
ddmmmyyyy

ADVERSE EVENTS		
Has the subject experienced any adverse events since last visit?	☐Yes	☐ No
Record all Adverse Events on Adverse Events CRF		

MEDICATIONS		
Have there been any changes to medications?	☐ Yes	☐ No
Record all medication on Concomitant Medications CRF		

VITAL SIGNS
See Vital Signs CRF for Days 1-3

COMPLETE NEUROLOGICAL EXAM
See Neurological Exam CRF for Days 1-3

WOUND EXAMINATION				
	Normal	***Abnormal***	***Not Done***	***Describe if abnormal or give reason not completed***
Wound Assessment	☐	☐	☐	

LABORATORY ANALYSIS

CBC with diff, plts **Date drawn** (ddmmmyyyy): _____

Test	*Resilts*		*Clinically Significant*
• Red blood cell count (RBC) o M: 4.40 – 5.80 x 10^6/cmm o F: 3.80 – 5.20 x 10^6/cmm	_____ x 10^6/cmm	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Hemoglobin (Hgb) o M: 13.5 – 17.0 g/dL o F: 11.3 – 15.2 g/dL	_____ g/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Hematocrit (Hct) o M: 39 – 50% o F: 33 – 45%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Platelet count (PLT) o 150- 400 x 10^3/cmm	_____ x 10^3/cmm	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• White blood cell count (WBC) o 4.0 – 11.0 x 10^3/cmm	_____ x 10^3/cmm	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Neutrophils • 35 – 73%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Lymphocytes o 15 – 52%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No

DAY 2 (cont.)

LABORATORY ANALYSIS

CBC with diff, plts (cont.)

Test	*Results*		*Clinically Significant*
▪ Monocytes o 4 – 13%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Basophils o 0 – 2%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Eosinophils o 0 – 5%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Mean corpuscular haemoglobin (MCH) o 27 – 33 pg	_____ pg	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Mean corpuscular haemoglobin concentration (MCHC) o 32 – 36 g/dL	_____ g/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Mean corpuscular volume (MCV) o 80 – 96 fL	_____ fL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No

LABORATORY ANALYSIS

Serum Chemistry **Date drawn** (ddmmmyyyy)**:**_____

Test	*Results*		*Clinically Significant*
• Sodium (Na) o 133 – 145 mEq/L	_____ mEq/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Potassium (K) o 3.1 – 5.1 mEq/L	_____ mEq/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Chloride (Cl) o 97 – 108 mEq/L	_____ mEq/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Bicarbonate (CO_2) o 22 – 32 mEq/L	_____ mEq/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Glucose o 70 – 100 mg/dL (fasting) o 70 – 200 mg/dL (non-fasting)	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Blood urea nitrogen (BUN) o 5 – 22 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Creatinine o M: 0.7 – 1.3 mg/dL o F: 0.4 – 1.2 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No

DAY 2 (cont.)

LABORATORY ANALYSIS **Serum Chemistry (cont.)**			
Test	***Results***		***Clinically Significant***
• Calcium (Ca) o 8.4 – 10.2 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Phosphorus o 2.4 – 5.0 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Total protein o 6.0 – 8.3 g/dL	_____ g/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Uric acid o M: 3.9 – 8.1 mg/dL o F: 2.0 – 6.9 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Gamma-glutamyl transferase (GGT) o 0 – 65 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Aspartate aminotransferase (AST) o 12 – 39 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Alanine aminotransferase (ALT) o 7 - 52 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Creatine kinase (CK) o M: 35 – 250 Units/L o F: 25 – 190 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Lactate dehydrogenase (LDH) o 120 – 240 Units/L	_____ IU/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Alkaline phosphatase (Alk Phos) o 39 – 117 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Total bilirubin o 0.3 – 1.4 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Cholesterol (Chol) o 100 – 200 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Triglycerides (TG) o 40 – 150 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Prothrombin time/INR (PT/INR) o 12.0 - 14.5 seconds	_____ seconds	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Partial thromboplastin time (PTT) o 25.0 – 35.0 seconds	_____ seconds	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No

DAY 2 (cont.)

LABORATORY ANALYSIS						
HSV Detection		**Date collected** (ddmmmyyyy)**:** _____				
Test	***Results***					***Clinically Significant***
Saliva	☐ Negative	☐ Positive	☐ Normal	☐ Abnormal	☐ Not done	☐ Yes ☐ No
Conjunctival	☐ Negative	☐ Positive	☐ Normal	☐ Abnormal	☐ Not done	☐ Yes ☐ No
Blood	☐ Negative	☐ Positive	☐ Normal	☐ Abnormal	☐ Not done	☐ Yes ☐ No

RESEARCH SAMPLES			
Date drawn (ddmmmyyyy): _____			
Test	***Yes***	***No***	***Comments***
LTA, Elispot-blood	☐	☐	
IFN Gamma Assay	☐	☐	
Blood for future research	☐	☐	

DAY 3 **Date:** _____
ddmmmyyyy

MRI
Date of procedure (ddmmmyyyy): _____
Was MRI completed prior to discharge? ☐ Yes ☐No Why? _____

ADVERSE EVENTS		
Has the subject experienced any adverse events since last visit?	☐Yes	☐ No
Record all Adverse Events on Adverse Events CRF		

MEDICATIONS		
Have there been any changes to medications?	☐ Yes	☐ No
Record all medication on Concomitant Medications CRF		

VITAL SIGNS
See Vital Signs CRF for Days 1-3

WOUND EXAMINATION				
	Normal	***Abnormal***	***Not Done***	***Describe if abnormal or give reason not completed***
Wound Assessment	☐	☐	☐	

COMPLETE NEUROLOGICAL EXAM
See Neurological Exam CRF for Days 1-3

KARNOFSKY PERFORMANCE SCALE	
Percent	***Description***
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 to do active work.
60	Requires occasional assistance, but is able to care for most of his/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.
0	Dead.
Karnofsky Performance Scale: _____%	

DAY 3 (cont.)

LABORATORY ANALYSIS			
HSV Detection		**Date collected** (ddmmmyyyy)**:** _____	
Test	***Results***		***Clinically Significant***
Blood	☐ Negative ☐ Positive	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No

RESEARCH SAMPLES			
Date drawn (ddmmmyyyy): _____			
Test	***Yes***	***No***	***Comments***
LTA, Elispot-blood	☐	☐	
IFN Gamma Assay	☐	☐	
Blood for future research	☐	☐	

I am confident that the information supplied in this case record form is complete and accurate data. I confirm that the Day 0 to Day 3 visits were conducted in accordance with the protocol and any protocol amendments and that written informed consent was obtained prior to the start of the study procedures.

_____ _____

PI or Co-PI Signature Date (ddmmmyyyy)

C134	Day 1 to Day 3	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

Vital Signs						
	Date dd/mmm/yyy	Time 24 hour clock	BP	HR bpm	RR	Temp °C
Pre-study drug administration						
1 hour						
2 hours						
3 hours						
4 hours						
5 hours						
6 hours						
7 hours						
8 hours						
9 hours						
10 hours						
11 hours						
12 hours						
14 hours						
16 hours						
18 hours						
20 hours						
22 hours						
24 hours						
28 hours						
32 hours						
36 hours						
40 hours						
44 hours						
48 hours						

C134	Day 1 to Day 3	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

COMPLETE NEUROLOGICAL EXAM

	Date/Time (ddmmmyyyy/ 24 hr clock)	Level of Consciousness	Orientation To			Muscle Strength *(enter corresponding number)* 0 = None 1 = Trace 2 = Gravity eliminated 3 = Against gravity 4 = Against resistance 5 = Normal	Gait Evaluation	Cranial Nerves Are any cranial nerves affected? (If yes, please circle which are affected)	Sensory Exam (performed as relevant to tumor location/signs/ symptoms) Are there abnormalities present? (if yes, describe)	Other Neuro-logical findings	Adverse Event(s) *If yes, record on AE page
			Time	Place	Self, person & others						
Pre-study drug admin		☐ Alert ☐ Sleepy, but easily aroused ☐ Somnolent/difficult to arouse ☐ Not arousable	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	Right Arm: _____ Right Leg: _____ Left Arm: _____ Left Leg: _____	☐ Normal ☐ Mildly ataxic ☐ Requires cane ☐ Non-ambulatory ☐ NA	Left: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII Right: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII	☐Yes _____ ☐No		☐Yes* ☐No
1 hour		☐ Alert ☐ Sleepy, but easily aroused ☐ Somnolent/difficult to arouse ☐ Not arousable	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	Right Arm: _____ Right Leg: _____ Left Arm: _____ Left Leg: _____	☐ Normal ☐ Mildly ataxic ☐ Requires cane ☐ Non-ambulatory ☐ NA	Left: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII Right: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII	☐Yes _____ ☐No		☐Yes* ☐No
2 hours		☐ Alert ☐ Sleepy, but easily aroused ☐ Somnolent/difficult to arouse ☐ Not arousable	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	Right Arm: _____ Right Leg: _____ Left Arm: _____ Left Leg: _____	☐ Normal ☐ Mildly ataxic ☐ Requires cane ☐ Non-ambulatory ☐ NA	Left: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII Right: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII	☐Yes _____ ☐No		☐Yes* ☐No
3 hours		☐ Alert ☐ Sleepy, but easily aroused ☐ Somnolent/difficult to arouse ☐ Not arousable	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	Right Arm: _____ Right Leg: _____ Left Arm: _____ Left Leg: _____	☐ Normal ☐ Mildly ataxic ☐ Requires cane ☐ Non-ambulatory ☐ NA	Left: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII Right: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII	☐Yes _____ ☐No		☐Yes* ☐No
4 hours		☐ Alert ☐ Sleepy, but easily aroused ☐ Somnolent/difficult to arouse ☐ Not arousable	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	Right Arm: _____ Right Leg: _____ Left Arm: _____ Left Leg: _____	☐ Normal ☐ Mildly ataxic ☐ Requires cane ☐ Non-ambulatory ☐ NA	Left: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII Right: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII	☐Yes _____ ☐No		☐Yes* ☐No
5 hours		☐ Alert ☐ Sleepy, but easily aroused ☐ Somnolent/difficult to arouse ☐ Not arousable	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	Right Arm: _____ Right Leg: _____ Left Arm: _____ Left Leg: _____	☐ Normal ☐ Mildly ataxic ☐ Requires cane ☐ Non-ambulatory ☐ NA	Left: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII Right: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII	☐Yes _____ ☐No		☐Yes* ☐No

C134	Day 1 to Day 3	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

COMPLETE NEUROLOGICAL EXAM (cont.)

	Date/Time (ddmmmyyyy/ 24 hr clock)	Level of Consciousness	Orientation To			Muscle Strength *(enter corresponding number)* 0 = None 1 = Trace 2 = Gravity eliminated 3 = Against gravity 4 = Against resistance 5 = Normal	Gait Evaluation	Cranial Nerves Are any cranial nerves affected? (If yes, please circle which are affected)	Sensory Exam (performed as relevant to tumor location/signs/ symptoms) Are there abnormalities present? (if yes, describe)	Other Neuro-logical findings	Adverse Event(s) *If yes, record on AE page
			Time	Place	Self, person & others						
6 hours		☐ Alert ☐ Sleepy, but easily aroused ☐ Somnolent/difficult to arouse ☐ Not arousable	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	Right Arm: _____ Right Leg: _____ Left Arm: _____ Left Leg: _____	☐ Normal ☐ Mildly ataxic ☐ Requires cane ☐ Non-ambulatory ☐ NA	Left: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII Right: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII	☐Yes _____ _____ _____ _____ ☐No		☐Yes* ☐No
7 hours		☐ Alert ☐ Sleepy, but easily aroused ☐ Somnolent/difficult to arouse ☐ Not arousable	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	Right Arm: _____ Right Leg: _____ Left Arm: _____ Left Leg: _____	☐ Normal ☐ Mildly ataxic ☐ Requires cane ☐ Non-ambulatory ☐ NA	Left: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII Right: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII	☐Yes _____ _____ _____ _____ ☐No		☐Yes* ☐No
8 hours		☐ Alert ☐ Sleepy, but easily aroused ☐ Somnolent/difficult to arouse ☐ Not arousable	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	Right Arm: _____ Right Leg: _____ Left Arm: _____ Left Leg: _____	☐ Normal ☐ Mildly ataxic ☐ Requires cane ☐ Non-ambulatory ☐ NA	Left: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII Right: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII	☐Yes _____ _____ _____ _____ ☐No		☐Yes* ☐No
9 hours		☐ Alert ☐ Sleepy, but easily aroused ☐ Somnolent/difficult to arouse ☐ Not arousable	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	Right Arm: _____ Right Leg: _____ Left Arm: _____ Left Leg: _____	☐ Normal ☐ Mildly ataxic ☐ Requires cane ☐ Non-ambulatory ☐ NA	Left: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII Right: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII	☐Yes _____ _____ _____ _____ ☐No		☐Yes* ☐No
10 hours		☐ Alert ☐ Sleepy, but easily aroused ☐ Somnolent/difficult to arouse ☐ Not arousable	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	Right Arm: _____ Right Leg: _____ Left Arm: _____ Left Leg: _____	☐ Normal ☐ Mildly ataxic ☐ Requires cane ☐ Non-ambulatory ☐ NA	Left: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII Right: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII	☐Yes _____ _____ _____ _____ ☐No		☐Yes* ☐No
11 hours		☐ Alert ☐ Sleepy, but easily aroused ☐ Somnolent/difficult to arouse ☐ Not arousable	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	Right Arm: _____ Right Leg: _____ Left Arm: _____ Left Leg: _____	☐ Normal ☐ Mildly ataxic ☐ Requires cane ☐ Non-ambulatory ☐ NA	Left: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII Right: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII	☐Yes _____ _____ _____ _____ ☐No		☐Yes* ☐No

C134	Day 1 to Day 3	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

COMPLETE NEUROLOGICAL EXAM (cont.)

	Date/Time (ddmmmyyyy/ 24 hr clock)	Level of Consciousness	Orientation To			Muscle Strength *(enter corresponding number)* 0 = None 1 = Trace 2 = Gravity eliminated 3 = Against gravity 4 = Against resistance 5 = Normal	Gait Evaluation	Cranial Nerves Are any cranial nerves affected? (If yes, please circle which are affected)	Sensory Exam (performed as relevant to tumor location/signs/ symptoms) Are there abnormalities present? (if yes, describe)	Other Neuro-logical findings	Adverse Event(s) *If yes, record on AE page
			Time	Place	Self, person & others						
12 hours		☐ Alert ☐ Sleepy, but easily aroused ☐ Somnolent/difficult to arouse ☐ Not arousable	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	Right Arm: _____ Right Leg: _____ Left Arm: _____ Left Leg: _____	☐ Normal ☐ Mildly ataxic ☐ Requires cane ☐ Non-ambulatory ☐ NA	Left: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII Right: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII	☐Yes _____ _____ _____ _____ ☐No		☐Yes* ☐No
14 hours		☐ Alert ☐ Sleepy, but easily aroused ☐ Somnolent/difficult to arouse ☐ Not arousable	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	Right Arm: _____ Right Leg: _____ Left Arm: _____ Left Leg: _____	☐ Normal ☐ Mildly ataxic ☐ Requires cane ☐ Non-ambulatory ☐ NA	Left: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII Right: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII	☐Yes _____ _____ _____ _____ ☐No		☐Yes* ☐No
16 hours		☐ Alert ☐ Sleepy, but easily aroused ☐ Somnolent/difficult to arouse ☐ Not arousable	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	Right Arm: _____ Right Leg: _____ Left Arm: _____ Left Leg: _____	☐ Normal ☐ Mildly ataxic ☐ Requires cane ☐ Non-ambulatory ☐ NA	Left: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII Right: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII	☐Yes _____ _____ _____ _____ ☐No		☐Yes* ☐No
18 hours		☐ Alert ☐ Sleepy, but easily aroused ☐ Somnolent/difficult to arouse ☐ Not arousable	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	Right Arm: _____ Right Leg: _____ Left Arm: _____ Left Leg: _____	☐ Normal ☐ Mildly ataxic ☐ Requires cane ☐ Non-ambulatory ☐ NA	Left: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII Right: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII	☐Yes _____ _____ _____ _____ ☐No		☐Yes* ☐No
20 hours		☐ Alert ☐ Sleepy, but easily aroused ☐ Somnolent/difficult to arouse ☐ Not arousable	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	Right Arm: _____ Right Leg: _____ Left Arm: _____ Left Leg: _____	☐ Normal ☐ Mildly ataxic ☐ Requires cane ☐ Non-ambulatory ☐ NA	Left: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII Right: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII	☐Yes _____ _____ _____ _____ ☐No		☐Yes* ☐No
22 hours		☐ Alert ☐ Sleepy, but easily aroused ☐ Somnolent/difficult to arouse ☐ Not arousable	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	Right Arm: _____ Right Leg: _____ Left Arm: _____ Left Leg: _____	☐ Normal ☐ Mildly ataxic ☐ Requires cane ☐ Non-ambulatory ☐ NA	Left: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII Right: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII	☐Yes _____ _____ _____ _____ ☐No		☐Yes* ☐No

C134	Day 1 to Day 3	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

COMPLETE NEUROLOGICAL EXAM (cont.)

	Date/Time (ddmmmyyyy/ 24 hr clock)	Level of Consciousness	Orientation To			Muscle Strength *(enter corresponding number)* 0 = None 1 = Trace 2 = Gravity eliminated 3 = Against gravity 4 = Against resistance 5 = Normal	Gait Evaluation	Cranial Nerves Are any cranial nerves affected? (If yes, please circle which are affected)	Sensory Exam (performed as relevant to tumor location/signs/ symptoms) Are there abnormalities present? (if yes, describe)	Other Neuro-logical findings	Adverse Event(s) *If yes, record on AE page
			Time	Place	Self, person & others						
24 hours		☐ Alert ☐ Sleepy, but easily aroused ☐ Somnolent/difficult to arouse ☐ Not arousable	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	Right Arm: _____ Right Leg: _____ Left Arm: _____ Left Leg: _____	☐ Normal ☐ Mildly ataxic ☐ Requires cane ☐ Non-ambulatory ☐ NA	Left: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII Right: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII	☐Yes _____ _____ _____ _____ ☐No		☐Yes* ☐No
28 hours		☐ Alert ☐ Sleepy, but easily aroused ☐ Somnolent/difficult to arouse ☐ Not arousable	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	Right Arm: _____ Right Leg: _____ Left Arm: _____ Left Leg: _____	☐ Normal ☐ Mildly ataxic ☐ Requires cane ☐ Non-ambulatory ☐ NA	Left: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII Right: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII	☐Yes _____ _____ _____ _____ ☐No		☐Yes* ☐No
32 hours		☐ Alert ☐ Sleepy, but easily aroused ☐ Somnolent/difficult to arouse ☐ Not arousable	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	Right Arm: _____ Right Leg: _____ Left Arm: _____ Left Leg: _____	☐ Normal ☐ Mildly ataxic ☐ Requires cane ☐ Non-ambulatory ☐ NA	Left: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII Right: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII	☐Yes _____ _____ _____ _____ ☐No		☐Yes* ☐No
36 hours		☐ Alert ☐ Sleepy, but easily aroused ☐ Somnolent/difficult to arouse ☐ Not arousable	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	Right Arm: _____ Right Leg: _____ Left Arm: _____ Left Leg: _____	☐ Normal ☐ Mildly ataxic ☐ Requires cane ☐ Non-ambulatory ☐ NA	Left: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII Right: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII	☐Yes _____ _____ _____ _____ ☐No		☐Yes* ☐No
40 hours		☐ Alert ☐ Sleepy, but easily aroused ☐ Somnolent/difficult to arouse ☐ Not arousable	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	Right Arm: _____ Right Leg: _____ Left Arm: _____ Left Leg: _____	☐ Normal ☐ Mildly ataxic ☐ Requires cane ☐ Non-ambulatory ☐ NA	Left: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII Right: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII	☐Yes _____ _____ _____ _____ ☐No		☐Yes* ☐No
44 hours		☐ Alert ☐ Sleepy, but easily aroused ☐ Somnolent/difficult to arouse ☐ Not arousable	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	Right Arm: _____ Right Leg: _____ Left Arm: _____ Left Leg: _____	☐ Normal ☐ Mildly ataxic ☐ Requires cane ☐ Non-ambulatory ☐ NA	Left: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII Right: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII	☐Yes _____ _____ _____ _____ ☐No		☐Yes* ☐No

C134	Day 1 to Day 3	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

COMPLETE NEUROLOGICAL EXAM (cont.)

	Date/Time (ddmmmyyyy/ 24 hr clock)	Level of Consciousness	Orientation To			Muscle Strength *(enter corresponding number)* 0 = None 1 = Trace 2 = Gravity eliminated 3 = Against gravity 4 = Against resistance 5 = Normal	Gait Evaluation	Cranial Nerves Are any cranial nerves affected? (If yes, please circle which are affected)	Sensory Exam (performed as relevant to tumor location/signs/ symptoms) Are there abnormalities present? (if yes, describe)	Other Neuro-logical findings	Adverse Event(s) *If yes, record on AE page
			Time	Place	Self, person & others						
48 hours		☐ Alert ☐ Sleepy, but easily aroused ☐ Somnolent/difficult to arouse ☐ Not arousable	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	Right Arm: _____ Right Leg: _____ Left Arm: _____ Left Leg: _____	☐ Normal ☐ Mildly ataxic ☐ Requires cane ☐ Non-ambulatory ☐ NA	Left: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII Right: ☐Yes ☐No II III IV V VI VII VIII IX X XI XII	☐Yes _____ _____ _____ _____ ☐No		☐Yes* ☐No

CATHETER/PUMP STATUS
(Record time using 24 hour clock)

Date (ddmmmyyyy): _____

Cohort/dose (pfu): ☐ $1x10^6$ ☐ $3x10^6$ ☐ $1x10^7$ ☐ $3x10^7$ ☐ $1x10^8$ Other:_____

Catheter/Pump A	Catheter/Pump B	Catheter/Pump C	Catheter/Pump D	Staff Initials
Flush (35 minutes):				
Start Time: _____ ☐ N/A Stop Time: _____ Amt. Infused: _____ml Rate: _____ml/hour	Start Time: _____ ☐ N/A Stop Time: _____ Amt. Infused: _____ml Rate: _____ml/hour	Start Time: _____ ☐ N/A Stop Time: _____ Amt. Infused: _____ml Rate: _____ml/hour	Start Time: _____ ☐ N/A Stop Time: _____ Amt. Infused: _____ml Rate: _____ml/hour	
First Infusion:				
Start Time: _____ ☐ N/A Stop Time: _____ Amt. Infused: _____ml Rate: _____ml/hour	Start Time: _____ ☐ N/A Stop Time: _____ Amt. Infused: _____ml Rate: _____ml/hour	Start Time: _____ ☐ N/A Stop Time: _____ Amt. Infused: _____ml Rate: _____ml/hour	Start Time: _____ ☐ N/A Stop Time: _____ Amt. Infused: _____ml Rate: _____ml/hour	

Was the total amount of Study Drug C134 Administered 1.2 ml? ☐ Yes ☐ No

If No, explain:_____

Was the total rate of administration 0.4 ml? ☐ Yes ☐ No

If No, explain:_____

Second Infusion:				
Start Time: _____ ☐ N/A Stop Time: _____ Amt. Infused: _____ml Rate: _____ml/hour	Start Time: _____ ☐ N/A Stop Time: _____ Amt. Infused: _____ml Rate: _____ml/hour	Start Time: _____ ☐ N/A Stop Time: _____ Amt. Infused: _____ml Rate: _____ml/hour	Start Time: _____ ☐ N/A Stop Time: _____ Amt. Infused: _____ml Rate: _____ml/hour	

Was the total amount of Study Drug C134 Administered 1.2 ml? ☐ Yes ☐ No

If No, explain:_____

Was the total rate of administration 0.4 ml? ☐ Yes ☐ No

If No, explain:_____

Was total dose of 2.4 ml of Study Drug C134 administered? ☐ Yes ☐ No

If No, explain:_____

Was Study Drug C134 given per protocol? ☐ Yes ☐ No

If No, explain:_____

DAY 10 (± 3 days) **Date**: _____
ddmmmyyyy

ADVERSE EVENTS		
Has the subject experienced any adverse events since last visit?	☐Yes	☐ No
Record all Adverse Events on Adverse Events CRF		

MEDICATIONS		
Have there been any changes to medications?	☐ Yes	☐ No
Record all medication on Concomitant Medications CRF		

VITAL SIGNS

Weight (kg): _____._____

Blood Pressure: _____/_____ Heart Rate: _____ bpm

Respiratory Rate: _____ Temperature: _____._____ °C

PHYSICAL EXAMINATION

System	*Normal*	*Abnormal*	*Not Done*	*Describe if abnormal or give reason not completed*
General Appearance	☐	☐	☐	
HEENT	☐	☐	☐	
Cardiovascular	☐	☐	☐	
Pulmonary	☐	☐	☐	
Abdomen	☐	☐	☐	
Musculoskeletal	☐	☐	☐	
Extremities	☐	☐	☐	
Lymph Nodes	☐	☐	☐	
Dermatology	☐	☐	☐	
Wound Assessment	☐	☐	☐	
Other, Specify _____	☐	☐	☐	

C134	Day 10 (± 3 days)	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

COMPLETE NEUROLOGICAL EXAM			
Level of Consciousness:	☐ Alert	☐Sleepy, but easily aroused	☐Somnolent/difficult to arouse ☐Not arousable
Orientation:	Oriented to time:	☐Yes ☐ No	
	Oriented to place:	☐Yes ☐ No	
	Oriented to self, person and others:	☐Yes ☐ No	
Muscle Strength: (enter corresponding number)	0 = None 1 = Trace 2 = Gravity eliminated 3 = Against gravity 4 = Against resistance 5 = Normal	Right Arm: _____ Left Arm: _____	Right Leg: _____ Left Leg: _____
Gait Evaluation:	☐ Normal ☐ Mildly ataxic	☐ Requires a cane	☐Non-ambulatory ☐Unable to evaluate
Cranial Nerves: Are any cranial nerves affected?	☐ Yes	Left: II III IV V VI VII VIII IX X XI XII Right: II III IV V VI VII VIII IX X XI XII	☐ No
Sensory Exam: Are there abnormalities present? (performed as relevant to tumor location/signs/ symptoms)	☐ Yes_____ ☐ No		
Other Neurological Findings:			
Comments:			

KARNOFSKY PERFORMANCE SCALE	
Percent	***Description***
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 to do active work.
60	Requires occasional assistance, but is able to care for most of his/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.
0	Dead.
Karnofsky Performance Scale: _____**%**	

C134	Day 10 (± 3 days)	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

LABORATORY ANALYSIS

CBC with diff, plts **Date drawn** (ddmmmyyyy)**:** _____

Test	*Results*		*Clinically Significant*
• Red blood cell count (RBC) o M: 4.40 – 5.80 x 10^6/cmm o F: 3.80 – 5.20 x 10^6/cmm	_____ x 10^6/cmm	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Hemoglobin (Hgb) o M: 13.5 – 17.0 g/dL o F: 11.3 – 15.2 g/dL	_____ g/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Hematocrit (Hct) o M: 39 – 50% o F: 33 – 45%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Platelet count (PLT) o 150- 400 x 10^3/cmm	_____ x 10^3/cmm	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• White blood cell count (WBC) o 4.0 – 11.0 x 10^3/cmm	_____ x 10^3/cmm	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Neutrophils • 35 – 73%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Lymphocytes o 15 – 52%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Monocytes o 4 – 13%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Basophils o 0 – 2%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Eosinophils o 0 – 5%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Mean corpuscular haemoglobin (MCH) o 27 – 33 pg	_____ pg	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Mean corpuscular haemoglobin concentration (MCHC) o 32 – 36 g/dL	_____ g/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Mean corpuscular volume (MCV) o 80 – 96 fL	_____ fL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No

LABORATORY ANALYSIS

Serum Chemistry **Date drawn** (ddmmmyyyy): _____

Test	*Results*		*Clinically Significant*
• Sodium (Na) o 133 – 145 mEq/L	_____ mEq/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Potassium (K) o 3.1 – 5.1 mEq/L	_____ mEq/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Chloride (Cl) o 97 – 108 mEq/L	_____ mEq/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Bicarbonate (CO_2) o 22 – 32 mEq/L	_____ mEq/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Glucose o 70 – 100 mg/dL (fasting) o 70 – 200 mg/dL (non-fasting)	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Blood urea nitrogen (BUN) o 5 – 22 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Creatinine o M: 0.7 – 1.3 mg/dL o F: 0.4 – 1.2 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Calcium (Ca) o 8.4 – 10.2 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Phosphorus o 2.4 – 5.0 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Total protein o 6.0 – 8.3 g/dL	_____ g/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Uric acid o M: 3.9 – 8.1 mg/dL o F: 2.0 – 6.9 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Gamma-glutamyl transferase (GGT) o 0 – 65 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Aspartate aminotransferase (AST) o 12 – 39 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Alanine aminotransferase (ALT) o 7 - 52 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Creatine kinase (CK) o M: 35 – 250 Units/L o F: 25 – 190 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No

C134	Day 10 (± 3 days)	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

LABORATORY ANALYSIS **Serum Chemistry (cont.)**			
Test	***Results***		***Clinically Significant***
• Lactate dehydrogenase (LDH) o 120 – 240 Units/L	_____ IU/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Alkaline phosphatase (Alk Phos) o 39 – 117 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Total bilirubin o 0.3 – 1.4 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Cholesterol (Chol) o 100 – 200 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Triglycerides (TG) o 40 – 150 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Prothrombin time/INR (PT/INR) o 12.0 - 14.5 seconds	_____ seconds	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Partial thromboplastin time (PTT) o 25.0 – 35.0 seconds	_____ seconds	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No

LABORATORY ANALYSIS **HSV Detection** **Date collected** (ddmmmyyyy)**:** _____					
Test	***Results***				***Clinically Significant***
Saliva	☐ Negative ☐ Positive	☐ Normal	☐ Abnormal	☐ Not done	☐ Yes ☐ No
Conjunctival	☐ Negative ☐ Positive	☐ Normal	☐ Abnormal	☐ Not done	☐ Yes ☐ No
Blood	☐ Negative ☐ Positive	☐ Normal	☐ Abnormal	☐ Not done	☐ Yes ☐ No

RESEARCH SAMPLES			
Date drawn (ddmmmyyyy): _____			
Test	***Yes***	***No***	***Comments***
HSV Antibody Titer	☐	☐	
LTA, Elispot-blood	☐	☐	
IFN Gamma Assay	☐	☐	
Blood for future research	☐	☐	

I am confident that the information supplied in this case record form is complete and accurate data. I confirm that the Day 10 Study Visit was conducted in accordance with the protocol and any protocol amendments and that written informed consent was obtained prior to the start of the study procedures.

_____ _____

PI or Co-PI Signature Date (ddmmmyyyy)

C134	Day 28 (± 4 days)	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

DAY 28 (± 4 days) **Date**: _____
ddmmmyyyy

MRI
Date of procedure (ddmmmyyyy): _____
Was MRI completed? ☐ Yes ☐No
If no, why? _____

ADVERSE EVENTS
Has the subject experienced any adverse events since last visit? ☐Yes ☐ No
Record all Adverse Events on Adverse Events CRF

MEDICATIONS
Have there been any changes to medications? ☐ Yes ☐ No
Record all medication on Concomitant Medications CRF

VITAL SIGNS
Weight (kg): _____._____
Blood Pressure: _____/_____ Heart Rate: _____ bpm
Respiratory Rate: _____ Temperature: _____._____ °C

PHYSICAL EXAMINATION				
System	***Normal***	***Abnormal***	***Not Done***	***Describe if abnormal or give reason not completed***
General Appearance	☐	☐	☐	
HEENT	☐	☐	☐	
Cardiovascular	☐	☐	☐	
Pulmonary	☐	☐	☐	
Abdomen	☐	☐	☐	
Musculoskeletal	☐	☐	☐	
Extremities	☐	☐	☐	
Lymph Nodes	☐	☐	☐	
Dermatology	☐	☐	☐	
Other, Specify _____	☐	☐	☐	

KARNOFSKY PERFORMANCE SCALE	
Percent	***Description***
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 to do active work.
60	Requires occasional assistance, but is able to care for most of his/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.
0	Dead.
Karnofsky Performance Scale: _____**%**	

COMPLETE NEUROLOGICAL EXAM	
Level of Consciousness:	☐ Alert ☐Sleepy, but easily aroused ☐Somnolent/difficult to arouse ☐Not arousable
Orientation:	Oriented to time: ☐Yes ☐ No Oriented to place: ☐Yes ☐ No Oriented to self, person and others: ☐Yes ☐ No
Muscle Strength: (enter corresponding number)	0 = None 1 = Trace 2 = Gravity eliminated 3 = Against gravity 4 = Against resistance 5 = Normal Right Arm: _____ Right Leg: _____ Left Arm: _____ Left Leg: _____
Gait Evaluation:	☐ Normal ☐ Mildly ataxic ☐ Requires a cane ☐Non-ambulatory ☐Unable to evaluate
Cranial Nerves: Are any cranial nerves affected?	☐ Yes Left: II III IV V VI VII VIII IX X XI XII Right: II III IV V VI VII VIII IX X XI XII ☐ No
Sensory Exam: Are there abnormalities present? (performed as relevant to tumor location/signs/ symptoms)	☐ Yes_____ ☐ No
Other Neurological Findings:	
Comments:	

LABORATORY ANALYSIS

CBC with diff, plts **Date drawn** (ddmmmyyyy): _____

Test	*Results*		*Clinically Significant*
• Red blood cell count (RBC) o M: 4.40 – 5.80 x 10^6/cmm o F: 3.80 – 5.20 x 10^6/cmm	_____ x 10^6/cmm	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Hemoglobin (Hgb) o M: 13.5 – 17.0 g/dL o F: 11.3 – 15.2 g/dL	_____ g/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Hematocrit (Hct) o M: 39 – 50% o F: 33 – 45%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Platelet count (PLT) o 150- 400 x 10^3/cmm	_____ x 10^3/cmm	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• White blood cell count (WBC) o 4.0 – 11.0 x 10^3/cmm	_____ x 10^3/cmm	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Neutrophils • 35 – 73%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Lymphocytes o 15 – 52%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Monocytes o 4 – 13%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Basophils o 0 – 2%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Eosinophils o 0 – 5%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Mean corpuscular haemoglobin (MCH) o 27 – 33 pg	_____ pg	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Mean corpuscular haemoglobin concentration (MCHC) o 32 – 36 g/dL	_____ g/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Mean corpuscular volume (MCV) o 80 – 96 fL	_____ fL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No

C134	Day 28 (± 4 days)	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

LABORATORY ANALYSIS

Serum Chemistry **Date drawn** (ddmmmyyyy)**:**

Test	*Results*		*Clinically Significant*
• Sodium (Na) o 133 – 145 mEq/L	_____ mEq/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Potassium (K) o 3.1 – 5.1 mEq/L	_____ mEq/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Chloride (Cl) o 97 – 108 mEq/L	_____ mEq/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Bicarbonate (CO_2) o 22 – 32 mEq/L	_____ mEq/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Glucose o 70 – 100 mg/dL (fasting) o 70 – 200 mg/dL (non-fasting)	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Blood urea nitrogen (BUN) o 5 – 22 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Creatinine o M: 0.7 – 1.3 mg/dL o F: 0.4 – 1.2 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Calcium (Ca) o 8.4 – 10.2 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Phosphorus o 2.4 – 5.0 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Total protein o 6.0 – 8.3 g/dL	_____ g/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Uric acid o M: 3.9 – 8.1 mg/dL o F: 2.0 – 6.9 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Gamma-glutamyl transferase (GGT) o 0 – 65 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Aspartate aminotransferase (AST) o 12 – 39 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Alanine aminotransferase (ALT) o 7 - 52 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Creatine kinase (CK) o M: 35 – 250 Units/L o F: 25 – 190 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No

C134	Day 28 (± 4 days)	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

LABORATORY ANALYSIS **Serum Chemistry (cont.)**			
Test	***Results***		***Clinically Significant***
• Lactate dehydrogenase (LDH) o 120 – 240 Units/L	_____ IU/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Alkaline phosphatase (Alk Phos) o 39 – 117 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Total bilirubin o 0.3 – 1.4 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Cholesterol (Chol) o 100 – 200 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Triglycerides (TG) o 40 – 150 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Prothrombin time/INR (PT/INR) o 12.0 - 14.5 seconds	_____ seconds	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Partial thromboplastin time (PTT) o 25.0 – 35.0 seconds	_____ seconds	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No

LABORATORY ANALYSIS **HSV Detection** **Date collected** (ddmmmyyyy)**:** _____			
Test	***Results***		***Clinically Significant***
Saliva	☐ Negative ☐ Positive	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
Conjunctival	☐ Negative ☐ Positive	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
Blood	☐ Negative ☐ Positive	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No

RESEARCH SAMPLES			
Date drawn (ddmmmyyyy): _____			
Test	***Yes***	***No***	***Comments***
HSV Antibody Titer	☐	☐	
LTA, Elispot-blood	☐	☐	
IFN Gamma Assay	☐	☐	
Blood for future research	☐	☐	

I am confident that the information supplied in this case record form is complete and accurate data. I confirm that the Day 28 Study Visit was conducted in accordance with the protocol and any protocol amendments and that written informed consent was obtained prior to the start of the study procedures.

_____ _____

PI or Co-PI Signature Date (ddmmmyyyy)

C134	Month 2 (± 12 days)	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

MONTH 2 (± 12 days) **Date:** _____
ddmmmyyyy

ADVERSE EVENTS		
Has the subject experienced any adverse events since last visit?	☐Yes	☐ No
Record all Adverse Events on Adverse Event CRF		

MEDICATIONS		
Have there been any changes to medications?	☐ Yes	☐ No
Record all medication on Concomitant Medications CRF		

LABORATORY ANALYSIS

CBC with diff, plts **Date drawn** (ddmmmyyyy): _____

Test	*Results*		*Clinically Significant*
• Red blood cell count (RBC) o M: 4.40 – 5.80 x 10^6/cmm o F: 3.80 – 5.20 x 10^6/cmm	_____ x 10^6/cmm	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Hemoglobin (Hgb) o M: 13.5 – 17.0 g/dL o F: 11.3 – 15.2 g/dL	_____ g/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Hematocrit (Hct) o M: 39 – 50% o F: 33 – 45%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Platelet count (PLT) o 150- 400 x 10^3/cmm	_____ x 10^3/cmm	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• White blood cell count (WBC) o 4.0 – 11.0 x 10^3/cmm	_____ x 10^3/cmm	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Neutrophils • 35 – 73%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Lymphocytes o 15 – 52%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Monocytes o 4 – 13%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Basophils o 0 – 2%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Eosinophils o 0 – 5%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Mean corpuscular haemoglobin (MCH) o 27 – 33 pg	_____ pg	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No

C134	Month 2 (± 12 days)	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

LABORATORY ANALYSIS

CBC with diff, plts (cont.)

Test	*Results*		*Clinically Significant*
• Mean corpuscular haemoglobin concentration (MCHC) o 32 – 36 g/dL	_____ g/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Mean corpuscular volume (MCV) o 80 – 96 fL	_____ fL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No

LABORATORY ANALYSIS

Serum Chemistry **Date drawn** (ddmmmyyyy): _____

Test	*Results*		*Clinically Significant*
• Sodium (Na) o 133 – 145 mEq/L	_____ mEq/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Potassium (K) o 3.1 – 5.1 mEq/L	_____ mEq/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Chloride (Cl) o 97 – 108 mEq/L	_____ mEq/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Bicarbonate (CO_2) o 22 – 32 mEq/L	_____ mEq/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Glucose o 70 – 100 mg/dL (fasting) o 70 – 200 mg/dL (non-fasting)	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Blood urea nitrogen (BUN) o 5 – 22 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Creatinine o M: 0.7 – 1.3 mg/dL o F: 0.4 – 1.2 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Calcium (Ca) o 8.4 – 10.2 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Phosphorus o 2.4 – 5.0 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Total protein o 6.0 – 8.3 g/dL	_____ g/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Uric acid o M: 3.9 – 8.1 mg/dL o F: 2.0 – 6.9 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Gamma-glutamyl transferase (GGT) o 0 – 65 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No

LABORATORY ANALYSIS

Serum Chemistry (cont.)

Test	*Results*		*Clinically Significant*
• Aspartate aminotransferase (AST) o 12 – 39 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Alanine aminotransferase (ALT) o 7 - 52 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Creatine kinase (CK) o M: 35 – 250 Units/L o F: 25 – 190 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Lactate dehydrogenase (LDH) o 120 – 240 Units/L	_____ IU/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Alkaline phosphatase (Alk Phos) o 39 – 117 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Total bilirubin o 0.3 – 1.4 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Cholesterol (Chol) o 100 – 200 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Triglycerides (TG) o 40 – 150 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Prothrombin time/INR (PT/INR) o 12.0 - 14.5 seconds	_____ seconds	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Partial thromboplastin time (PTT) o 25.0 – 35.0 seconds	_____ seconds	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No

LABORATORY ANALYSIS

HSV Detection **Date collected** (ddmmmyyyy)**:** _____

Test	*Results*		*Clinically Significant*
Saliva	☐ Negative ☐ Positive	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
Conjunctival	☐ Negative ☐ Positive	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
Blood	☐ Negative ☐ Positive	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No

I am confident that the information supplied in this case record form is complete and accurate data. I confirm that the Month 2 Study Visit was conducted in accordance with the protocol and any protocol amendments and that written informed consent was obtained prior to the start of the study procedures.

PI or Co-PI Signature _____ Date (ddmmmyyy _____

MONTH 3 (± 12 days) **Date:** _____
ddmmmyyyy

MRI
Date of procedure (ddmmmyyyy): _____
Was MRI completed? ☐ Yes ☐No
If no, why? _____

ADVERSE EVENTS
Has the subject experienced any adverse events since last visit? ☐Yes ☐ No
Record all Adverse Events on Adverse Event CRF

MEDICATIONS
Have there been any changes to medications? ☐ Yes ☐ No
Record all medication on Concomitant Medications CRF

VITAL SIGNS
Weight (kg): _____._____
Blood Pressure: _____/_____ Heart Rate: _____ bpm
Respiratory Rate: _____ Temperature: _____._____ °C

PHYSICAL EXAMINATION				
System	***Normal***	***Abnormal***	***Not Done***	***Describe if abnormal or give reason not completed***
General Appearance	☐	☐	☐	
HEENT	☐	☐	☐	
Cardiovascular	☐	☐	☐	
Pulmonary	☐	☐	☐	
Abdomen	☐	☐	☐	
Musculoskeletal	☐	☐	☐	
Extremities	☐	☐	☐	
Lymph Nodes	☐	☐	☐	
Dermatology	☐	☐	☐	
Other, Specify _____	☐	☐	☐	

C134	Month 3 (± 12 days)	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

KARNOFSKY PERFORMANCE SCALE	
Percent	***Description***
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 to do active work.
60	Requires occasional assistance, but is able to care for most of his/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.
0	Dead.

Karnofsky Performance Scale: _____%

COMPLETE NEUROLOGICAL EXAM

Level of Consciousness: ☐ Alert ☐Sleepy, but easily aroused ☐Somnolent/difficult to arouse ☐Not arousable

Orientation:

Oriented to time:	☐Yes	☐ No
Oriented to place:	☐Yes	☐ No
Oriented to self, person and others:	☐Yes	☐ No

Muscle Strength: (enter corresponding number)

0 = None
1 = Trace
2 = Gravity eliminated
3 = Against gravity
4 = Against resistance
5 = Normal

Right Arm: _____ Right Leg: _____

Left Arm: _____ Left Leg: _____

Gait Evaluation: ☐ Normal ☐ Mildly ataxic ☐ Requires a cane ☐Non-ambulatory ☐Unable to evaluate

Cranial Nerves: Are any cranial nerves affected? ☐ Yes ☐ No

Left: II III IV V VI VII VIII IX X XI XII

Right: II III IV V VI VII VIII IX X XI XII

Sensory Exam: Are there abnormalities present? (performed as relevant to tumor location/signs/ symptoms)

☐ Yes_____

☐ No

Other Neurological Findings:

Comments:

C134	Month 3 (± 12 days)	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

LABORATORY ANALYSIS

CBC with diff, plts **Date drawn** (ddmmmyyyy): _____

Test	*Results*		*Clinically Significant*
• Red blood cell count (RBC) o M: 4.40 – 5.80 x 10^6/cmm o F: 3.80 – 5.20 x 10^6/cmm	_____ x 10^6/cmm	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Hemoglobin (Hgb) o M: 13.5 – 17.0 g/dL o F: 11.3 – 15.2 g/dL	_____ g/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Hematocrit (Hct) o M: 39 – 50% o F: 33 – 45%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Platelet count (PLT) o 150- 400 x 10^3/cmm	_____ x 10^3/cmm	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• White blood cell count (WBC) o 4.0 – 11.0 x 10^3/cmm	_____ x 10^3/cmm	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Neutrophils • 35 – 73%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Lymphocytes o 15 – 52%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Monocytes o 4 – 13%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Basophils o 0 – 2%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Eosinophils o 0 – 5%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Mean corpuscular haemoglobin (MCH) o 27 – 33 pg	_____ pg	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Mean corpuscular haemoglobin concentration (MCHC) o 32 – 36 g/dL	_____ g/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Mean corpuscular volume (MCV) o 80 – 96 fL	_____ fL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No

C134	Month 3 (± 12 days)	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

LABORATORY ANALYSIS

Serum Chemistry **Date drawn** (ddmmmyyyy)**:**

Test	*Results*		*Clinically Significant*
• Sodium (Na) o 133 – 145 mEq/L	_____ mEq/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Potassium (K) o 3.1 – 5.1 mEq/L	_____ mEq/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Chloride (Cl) o 97 – 108 mEq/L	_____ mEq/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Bicarbonate (CO_2) o 22 – 32 mEq/L	_____ mEq/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Glucose o 70 – 100 mg/dL (fasting) o 70 – 200 mg/dL (non-fasting)	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Blood urea nitrogen (BUN) o 5 – 22 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Creatinine o M: 0.7 – 1.3 mg/dL o F: 0.4 – 1.2 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Calcium (Ca) o 8.4 – 10.2 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Phosphorus o 2.4 – 5.0 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Total protein o 6.0 – 8.3 g/dL	_____ g/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Uric acid o M: 3.9 – 8.1 mg/dL o F: 2.0 – 6.9 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Gamma-glutamyl transferase (GGT) o 0 – 65 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Aspartate aminotransferase (AST) o 12 – 39 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Alanine aminotransferase (ALT) o 7 – 52 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Creatine kinase (CK) o M: 35 – 250 Units/L o F: 25 – 190 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No

C134	Month 3 (± 12 days)	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

LABORATORY ANALYSIS **Serum Chemistry (cont.)**			
Test	***Results***		***Clinically Significant***
• Lactate dehydrogenase (LDH) o 120 – 240 Units/L	_____ IU/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Alkaline phosphatase (Alk Phos) o 39 – 117 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Total bilirubin o 0.3 – 1.4 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Cholesterol (Chol) o 100 – 200 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Triglycerides (TG) o 40 – 150 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Prothrombin time/INR (PT/INR) o 12.0 - 14.5 seconds	_____ seconds	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Partial thromboplastin time (PTT) o 25.0 – 35.0 seconds	_____ seconds	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No

LABORATORY ANALYSIS **HSV Detection** **Date collected** (ddmmmyyyy)**:** _____					
Test	***Results***				***Clinically Significant***
Saliva	☐ Negative ☐ Positive	☐ Normal	☐ Abnormal	☐ Not done	☐ Yes ☐ No
Conjunctival	☐ Negative ☐ Positive	☐ Normal	☐ Abnormal	☐ Not done	☐ Yes ☐ No
Blood	☐ Negative ☐ Positive	☐ Normal	☐ Abnormal	☐ Not done	☐ Yes ☐ No

RESEARCH SAMPLES			
Date drawn (ddmmmyyyy): _____			
Test	***Yes***	***No***	***Comments***
HSV Antibody Titer	☐	☐	
LTA, Elispot-blood	☐	☐	
IFN Gamma Assay	☐	☐	
Blood for future research	☐	☐	

I am confident that the information supplied in this case record form is complete and accurate data. I confirm that the Month 3 Study Visit was conducted in accordance with the protocol and any protocol amendments and that written informed consent was obtained prior to the start of the study procedures.

_____ _____

PI or Co-PI Signature Date (ddmmmyyyy)

C134	Month 4 (± 12 days)	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

MONTH 4 (± 12 days) **Date:** _____
ddmmmyyyy

ADVERSE EVENTS		
Has the subject experienced any adverse events since last visit?	☐Yes	☐ No
Record all Adverse Events on Adverse Event CRF		

MEDICATIONS		
Have there been any changes to medications?	☐ Yes	☐ No
Record all medication on Concomitant Medications CRF		

LABORATORY ANALYSIS

CBC with diff, plts **Date drawn** (ddmmmyyyy): _____

Test	*Results*		*Clinically Significant*
• Red blood cell count (RBC) o M: 4.40 – 5.80 x 10^6/cmm o F: 3.80 – 5.20 x 10^6/cmm	_____ x 10^6/cmm	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Hemoglobin (Hgb) o M: 13.5 – 17.0 g/dL o F: 11.3 – 15.2 g/dL	_____ g/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Hematocrit (Hct) o M: 39 – 50% o F: 33 – 45%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Platelet count (PLT) o 150- 400 x 10^3/cmm	_____ x 10^3/cmm	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• White blood cell count (WBC) o 4.0 – 11.0 x 10^3/cmm	_____ x 10^3/cmm	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Neutrophils • 35 – 73%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Lymphocytes o 15 – 52%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Monocytes o 4 – 13%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Basophils o 0 – 2%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Eosinophils o 0 – 5%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Mean corpuscular haemoglobin (MCH) o 27 – 33 pg	_____ pg	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No

C134	Month 4 (± 12 days)	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

LABORATORY ANALYSIS

CBC with diff, plts (cont.)

Test	*Results*		*Clinically Significant*
• Mean corpuscular haemoglobin concentration (MCHC) o 32 – 36 g/dL	_____ g/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Mean corpuscular volume (MCV) o 80 – 96 fL	_____ fL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No

LABORATORY ANALYSIS

Serum Chemistry **Date drawn** (ddmmmyyyy)**:** _____

Test	*Results*		*Clinically Significant*
• Sodium (Na) o 133 – 145 mEq/L	_____ mEq/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Potassium (K) o 3.1 – 5.1 mEq/L	_____ mEq/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Chloride (Cl) o 97 – 108 mEq/L	_____ mEq/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Bicarbonate (CO_2) o 22 – 32 mEq/L	_____ mEq/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Glucose o 70 – 100 mg/dL (fasting) o 70 – 200 mg/dL (non-fasting)	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Blood urea nitrogen (BUN) o 5 – 22 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Creatinine o M: 0.7 – 1.3 mg/dL o F: 0.4 – 1.2 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Calcium (Ca) o 8.4 – 10.2 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Phosphorus o 2.4 – 5.0 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Total protein o 6.0 – 8.3 g/dL	_____ g/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Uric acid o M: 3.9 – 8.1 mg/dL o F: 2.0 – 6.9 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Gamma-glutamyl transferase (GGT) o 0 – 65 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No

LABORATORY ANALYSIS

Serum Chemistry (cont.)

Test	*Results*		*Clinically Significant*
• Aspartate aminotransferase (AST) o 12 – 39 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Alanine aminotransferase (ALT) o 7 – 52 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Creatine kinase (CK) o M: 35 – 250 Units/L o F: 25 – 190 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Lactate dehydrogenase (LDH) o 120 – 240 Units/L	_____ IU/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Alkaline phosphatase (Alk Phos) o 39 – 117 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Total bilirubin o 0.3 – 1.4 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Cholesterol (Chol) o 100 – 200 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Triglycerides (TG) o 40 – 150 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Prothrombin time/INR (PT/INR) o 12.0 - 14.5 seconds	_____ seconds	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Partial thromboplastin time (PTT) o 25.0 – 35.0 seconds	_____ seconds	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No

LABORATORY ANALYSIS

HSV Detection **Date collected** (ddmmmyyyy): _____

Test	*Results*					*Clinically Significant*
Saliva	☐ Negative	☐ Positive	☐ Normal	☐ Abnormal	☐ Not done	☐ Yes ☐ No
Conjunctival	☐ Negative	☐ Positive	☐ Normal	☐ Abnormal	☐ Not done	☐ Yes ☐ No
Blood	☐ Negative	☐ Positive	☐ Normal	☐ Abnormal	☐ Not done	☐ Yes ☐ No

I am confident that the information supplied in this case record form is complete and accurate data. I confirm that the Month 4 Study Visit was conducted in accordance with the protocol and any protocol amendments and that written informed consent was obtained prior to the start of the study procedures.

PI or Co-PI Signature _____ Date (ddmmmyyy _____

C134	Month 5 (± 12 days)	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

MONTH 5 (± 12 days) **Date:** _____
ddmmmyyyy

ADVERSE EVENTS		
Has the subject experienced any adverse events since last visit?	☐Yes	☐ No
Record all Adverse Events on Adverse Event CRF		

MEDICATIONS		
Have there been any changes to medications?	☐ Yes	☐ No
Record all medication on Concomitant Medications CRF		

LABORATORY ANALYSIS

CBC with diff, plts **Date drawn** (ddmmmyyyy): _____

Test	*Results*		*Clinically Significant*
• Red blood cell count (RBC) o M: 4.40 – 5.80 x 10^6/cmm o F: 3.80 – 5.20 x 10^6/cmm	_____ x 10^6/cmm	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Hemoglobin (Hgb) o M: 13.5 – 17.0 g/dL o F: 11.3 – 15.2 g/dL	_____ g/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Hematocrit (Hct) o M: 39 – 50% o F: 33 – 45%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Platelet count (PLT) o 150- 400 x 10^3/cmm	_____ x 10^3/cmm	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• White blood cell count (WBC) o 4.0 – 11.0 x 10^3/cmm	_____ x 10^3/cmm	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Neutrophils • 35 – 73%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Lymphocytes o 15 – 52%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Monocytes o 4 – 13%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Basophils o 0 – 2%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Eosinophils o 0 – 5%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Mean corpuscular haemoglobin (MCH) o 27 – 33 pg	_____ pg	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No

C134	Month 5 (± 12 days)	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

LABORATORY ANALYSIS CBC with diff, plts (cont.)			
Test	***Results***		***Clinically Significant***
• Mean corpuscular haemoglobin concentration (MCHC) o 32 – 36 g/dL	_____ g/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Mean corpuscular volume (MCV) o 80 – 96 fL	_____ fL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No

LABORATORY ANALYSIS **Serum Chemistry** **Date drawn** (ddmmmyyyy)**:** _____			
Test	***Results***		***Clinically Significant***
• Sodium (Na) o 133 – 145 mEq/L	_____ mEq/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Potassium (K) o 3.1 – 5.1 mEq/L	_____ mEq/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Chloride (Cl) o 97 – 108 mEq/L	_____ mEq/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Bicarbonate (CO_2) o 22 – 32 mEq/L	_____ mEq/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Glucose o 70 – 100 mg/dL (fasting) o 70 – 200 mg/dL (non-fasting)	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Blood urea nitrogen (BUN) o 5 – 22 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Creatinine o M: 0.7 – 1.3 mg/dL o F: 0.4 – 1.2 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Calcium (Ca) o 8.4 – 10.2 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Phosphorus o 2.4 – 5.0 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Total protein o 6.0 – 8.3 g/dL	_____ g/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Uric acid o M: 3.9 – 8.1 mg/dL o F: 2.0 – 6.9 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Gamma-glutamyl transferase (GGT) o 0 – 65 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No

LABORATORY ANALYSIS

Serum Chemistry (cont.)

Test	*Results*		*Clinically Significant*
• Aspartate aminotransferase (AST) o 12 – 39 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Alanine aminotransferase (ALT) o 7 - 52 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Creatine kinase (CK) o M: 35 – 250 Units/L o F: 25 – 190 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Lactate dehydrogenase (LDH) o 120 – 240 Units/L	_____ IU/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Alkaline phosphatase (Alk Phos) o 39 – 117 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Total bilirubin o 0.3 – 1.4 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Cholesterol (Chol) o 100 – 200 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Triglycerides (TG) o 40 – 150 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Prothrombin time/INR (PT/INR) o 12.0 - 14.5 seconds	_____ seconds	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Partial thromboplastin time (PTT) o 25.0 – 35.0 seconds	_____ seconds	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No

LABORATORY ANALYSIS

HSV Detection **Date collected** (ddmmmyyyy): _____

Test	*Results*		*Clinically Significant*
Saliva	☐ Negative ☐ Positive	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
Conjunctival	☐ Negative ☐ Positive	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
Blood	☐ Negative ☐ Positive	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No

I am confident that the information supplied in this case record form is complete and accurate data. I confirm that the Month 5 Study Visit was conducted in accordance with the protocol and any protocol amendments and that written informed consent was obtained prior to the start of the study procedures.

PI or Co-PI Signature _____ Date (ddmmmyyy _____

C134	Month 6 (± 12 days)	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

MONTH 6 (± 12 days) **Date:** _____
ddmmmyyyy

MRI
Date of procedure (ddmmmyyyy): _____
Was MRI completed? ☐ Yes ☐No
If no, why? _____

ADVERSE EVENTS
Has the subject experienced any adverse events since last visit? ☐Yes ☐ No
Record all Adverse Events on Adverse Event CRF

MEDICATIONS
Have there been any changes to medications? ☐ Yes ☐ No
Record all medication on Concomitant Medications CRF

VITAL SIGNS
Weight (kg): _____._____
Blood Pressure: _____/_____ Heart Rate: _____ bpm
Respiratory Rate: _____ Temperature: _____._____ °C

PHYSICAL EXAMINATION

System	*Normal*	*Abnormal*	*Not Done*	*Describe if abnormal or give reason not completed*
General Appearance	☐	☐	☐	
HEENT	☐	☐	☐	
Cardiovascular	☐	☐	☐	
Pulmonary	☐	☐	☐	
Abdomen	☐	☐	☐	
Musculoskeletal	☐	☐	☐	
Extremities	☐	☐	☐	
Lymph Nodes	☐	☐	☐	
Dermatology	☐	☐	☐	
Other, Specify _____	☐	☐	☐	

C134	Month 6 (± 12 days)	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

COMPLETE NEUROLOGICAL EXAM		
Level of Consciousness:	☐ Alert ☐Sleepy, but easily aroused ☐Somnolent/difficult to arouse ☐Not arousable	
Orientation:	Oriented to time:	☐Yes ☐ No
	Oriented to place:	☐Yes ☐ No
	Oriented to self, person and others:	☐Yes ☐ No
Muscle Strength: (enter corresponding number)	0 = None 1 = Trace 2 = Gravity eliminated 3 = Against gravity 4 = Against resistance 5 = Normal	Right Arm: _____ Right Leg: _____ Left Arm: _____ Left Leg: _____
Gait Evaluation:	☐ Normal ☐ Mildly ataxic ☐ Requires a cane ☐Non-ambulatory ☐Unable to evaluate	
Cranial Nerves: Are any cranial nerves affected?	☐ Yes	Left: II III IV V VI VII VIII IX X XI XII Right: II III IV V VI VII VIII IX X XI XII ☐ No
Sensory Exam: Are there abnormalities present? (performed as relevant to tumor location/signs/ symptoms)	☐ Yes_____ ☐ No	
Other Neurological Findings:		
Comments:		

KARNOFSKY PERFORMANCE SCALE	
Percent	***Description***
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 to do active work.
60	Requires occasional assistance, but is able to care for most of his/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.
0	Dead.
Karnofsky Performance Scale: _____%	

C134	Month 6 (± 12 days)	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

LABORATORY ANALYSIS

CBC with diff, plts **Date drawn** (ddmmmyyyy)**:** _____

Test	*Results*		*Clinically Significant*
• Red blood cell count (RBC) o M: 4.40 – 5.80 x 10^6/cmm o F: 3.80 – 5.20 x 10^6/cmm	_____ x 10^6/cmm	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Hemoglobin (Hgb) o M: 13.5 – 17.0 g/dL o F: 11.3 – 15.2 g/dL	_____ g/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Hematocrit (Hct) o M: 39 – 50% o F: 33 – 45%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Platelet count (PLT) o 150- 400 x 10^3/cmm	_____ x 10^3/cmm	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• White blood cell count (WBC) o 4.0 – 11.0 x 10^3/cmm	_____ x 10^3/cmm	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Neutrophils • 35 – 73%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Lymphocytes o 15 – 52%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Monocytes o 4 – 13%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Basophils o 0 – 2%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Eosinophils o 0 – 5%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Mean corpuscular haemoglobin (MCH) o 27 – 33 pg	_____ pg	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Mean corpuscular haemoglobin concentration (MCHC) o 32 – 36 g/dL	_____ g/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Mean corpuscular volume (MCV) o 80 – 96 fL	_____ fL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No

C134	Month 6 (± 12 days)	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

LABORATORY ANALYSIS

Serum Chemistry **Date drawn** (ddmmmyyyy)**:**

Test	*Results*		*Clinically Significant*
• Sodium (Na) o 133 – 145 mEq/L	_____ mEq/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Potassium (K) o 3.1 – 5.1 mEq/L	_____ mEq/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Chloride (Cl) o 97 – 108 mEq/L	_____ mEq/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Bicarbonate (CO_2) o 22 – 32 mEq/L	_____ mEq/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Glucose o 70 – 100 mg/dL (fasting) o 70 – 200 mg/dL (non-fasting)	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Blood urea nitrogen (BUN) o 5 – 22 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Creatinine o M: 0.7 – 1.3 mg/dL o F: 0.4 – 1.2 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Calcium (Ca) o 8.4 – 10.2 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Phosphorus o 2.4 – 5.0 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Total protein o 6.0 – 8.3 g/dL	_____ g/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Uric acid o M: 3.9 – 8.1 mg/dL o F: 2.0 – 6.9 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Gamma-glutamyl transferase (GGT) o 0 – 65 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Aspartate aminotransferase (AST) o 12 – 39 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Alanine aminotransferase (ALT) o 7 - 52 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Creatine kinase (CK) o M: 35 – 250 Units/L o F: 25 – 190 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No

C134	Month 6 (± 12 days)	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

LABORATORY ANALYSIS

Serum Chemistry (cont.)

Test	*Results*		*Clinically Significant*
• Lactate dehydrogenase (LDH) o 120 – 240 Units/L	_____ IU/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Alkaline phosphatase (Alk Phos) o 39 – 117 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Total bilirubin o 0.3 – 1.4 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Cholesterol (Chol) o 100 – 200 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Triglycerides (TG) o 40 – 150 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Prothrombin time/INR (PT/INR) o 12.0 - 14.5 seconds	_____ seconds	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Partial thromboplastin time (PTT) o 25.0 – 35.0 seconds	_____ seconds	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No

LABORATORY ANALYSIS

HSV Detection **Date collected** (ddmmmyyyy): _____

Test	*Results*					*Clinically Significant*
Saliva	☐ Negative	☐ Positive	☐ Normal	☐ Abnormal	☐ Not done	☐ Yes ☐ No
Conjunctival	☐ Negative	☐ Positive	☐ Normal	☐ Abnormal	☐ Not done	☐ Yes ☐ No
Blood	☐ Negative	☐ Positive	☐ Normal	☐ Abnormal	☐ Not done	☐ Yes ☐ No

RESEARCH SAMPLES

Date drawn (ddmmmyyyy)**:** _____

Test	*Yes*	*No*	*Comments*
HSV Antibody Titer	☐	☐	
LTA, Elispot-blood	☐	☐	
IFN Gamma Assay	☐	☐	
Blood for future research	☐	☐	

I am confident that the information supplied in this case record form is complete and accurate data. I confirm that the Month 6 Study Visit was conducted in accordance with the protocol and any protocol amendments and that written informed consent was obtained prior to the start of the study procedures.

_____ _____

PI or Co-PI Signature Date (ddmmmyyyy)

C134	Month 9 (± 12 days)	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

MONTH 9 (± 12 days) **Date:** _____
ddmmmyyyy

MRI
Date of procedure (ddmmmyyyy): _____
Was MRI completed? ☐ Yes ☐No
If no, why? _____

ADVERSE EVENTS
Has the subject experienced any adverse events since last visit? ☐Yes ☐ No
Record all Adverse Events on Adverse Event CRF

MEDICATIONS
Have there been any changes to medications? ☐ Yes ☐ No
Record all medication on Concomitant Medications CRF

VITAL SIGNS
Weight (kg): _____._____
Blood Pressure: _____/_____ Heart Rate: _____ bpm
Respiratory Rate: _____ Temperature: _____._____ °C

PHYSICAL EXAMINATION

System	*Normal*	*Abnormal*	*Not Done*	*Describe if abnormal or give reason not completed*
General Appearance	☐	☐	☐	
HEENT	☐	☐	☐	
Cardiovascular	☐	☐	☐	
Pulmonary	☐	☐	☐	
Abdomen	☐	☐	☐	
Musculoskeletal	☐	☐	☐	
Extremities	☐	☐	☐	
Lymph Nodes	☐	☐	☐	
Dermatology	☐	☐	☐	
Other, Specify _____	☐	☐	☐	

C134	Month 9 (± 12 days)	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

COMPLETE NEUROLOGICAL EXAM		
Level of Consciousness:	☐ Alert ☐Sleepy, but easily aroused ☐Somnolent/difficult to arouse ☐Not arousable	
Orientation:	Oriented to time: ☐Yes ☐ No Oriented to place: ☐Yes ☐ No Oriented to self, person and others: ☐Yes ☐ No	
Muscle Strength: (enter corresponding number)	0 = None 1 = Trace 2 = Gravity eliminated 3 = Against gravity 4 = Against resistance 5 = Normal	Right Arm: _____ Right Leg: _____ Left Arm: _____ Left Leg: _____
Gait Evaluation:	☐ Normal ☐ Mildly ataxic ☐ Requires a cane ☐Non-ambulatory ☐Unable to evaluate	
Cranial Nerves: Are any cranial nerves affected?	☐ Yes	Left: II III IV V VI VII VIII IX X XI XII Right: II III IV V VI VII VIII IX X XI XII ☐ No
Sensory Exam: Are there abnormalities present? (performed as relevant to tumor location/signs/ symptoms)	☐ Yes_____ ☐ No	
Other Neurological Findings:		
Comments:		

KARNOFSKY PERFORMANCE SCALE	
Percent	***Description***
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 to do active work.
60	Requires occasional assistance, but is able to care for most of his/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.
0	Dead.
Karnofsky Performance Scale: _____%	

C134	Month 9 (± 12 days)	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

LABORATORY ANALYSIS

CBC with diff, plts **Date drawn** (ddmmmyyyy): _____

Test	*Results*		*Clinically Significant*
• Red blood cell count (RBC) o M: 4.40 – 5.80 x 10^6/cmm o F: 3.80 – 5.20 x 10^6/cmm	_____ x 10^6/cmm	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Hemoglobin (Hgb) o M: 13.5 – 17.0 g/dL o F: 11.3 – 15.2 g/dL	_____ g/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Hematocrit (Hct) o M: 39 – 50% o F: 33 – 45%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Platelet count (PLT) o 150- 400 x 10^3/cmm	_____ x 10^3/cmm	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• White blood cell count (WBC) o 4.0 – 11.0 x 10^3/cmm	_____ x 10^3/cmm	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Neutrophils • 35 – 73%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Lymphocytes o 15 – 52%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Monocytes o 4 – 13%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Basophils o 0 – 2%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Eosinophils o 0 – 5%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Mean corpuscular haemoglobin (MCH) o 27 – 33 pg	_____ pg	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Mean corpuscular haemoglobin concentration (MCHC) o 32 – 36 g/dL	_____ g/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Mean corpuscular volume (MCV) o 80 – 96 fL	_____ fL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No

C134	Month 9 (± 12 days)	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

LABORATORY ANALYSIS

Serum Chemistry **Date drawn** (ddmmmyyyy)**:**

Test	*Results*		*Clinically Significant*
• Sodium (Na) o 133 – 145 mEq/L	_____ mEq/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Potassium (K) o 3.1 – 5.1 mEq/L	_____ mEq/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Chloride (Cl) o 97 – 108 mEq/L	_____ mEq/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Bicarbonate (CO_2) o 22 – 32 mEq/L	_____ mEq/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Glucose o 70 – 100 mg/dL (fasting) o 70 – 200 mg/dL (non-fasting)	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Blood urea nitrogen (BUN) o 5 – 22 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Creatinine o M: 0.7 – 1.3 mg/dL o F: 0.4 – 1.2 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Calcium (Ca) o 8.4 – 10.2 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Phosphorus o 2.4 – 5.0 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Total protein o 6.0 – 8.3 g/dL	_____ g/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Uric acid o M: 3.9 – 8.1 mg/dL o F: 2.0 – 6.9 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Gamma-glutamyl transferase (GGT) o 0 – 65 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Aspartate aminotransferase (AST) o 12 – 39 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Alanine aminotransferase (ALT) o 7 - 52 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Creatine kinase (CK) o M: 35 – 250 Units/L o F: 25 – 190 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No

C134	Month 9 (± 12 days)	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

LABORATORY ANALYSIS

Serum Chemistry (cont.)

Test	*Results*		*Clinically Significant*
• Lactate dehydrogenase (LDH) o 120 – 240 Units/L	_____ IU/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Alkaline phosphatase (Alk Phos) o 39 – 117 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Total bilirubin o 0.3 – 1.4 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Cholesterol (Chol) o 100 – 200 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Triglycerides (TG) o 40 – 150 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Prothrombin time/INR (PT/INR) o 12.0 - 14.5 seconds	_____ seconds	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Partial thromboplastin time (PTT) o 25.0 – 35.0 seconds	_____ seconds	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No

LABORATORY ANALYSIS

HSV Detection **Date collected** (ddmmmyyyy):

Test	*Results*					*Clinically Significant*
Saliva	☐ Negative	☐ Positive	☐ Normal	☐ Abnormal	☐ Not done	☐ Yes ☐ No
Conjunctival	☐ Negative	☐ Positive	☐ Normal	☐ Abnormal	☐ Not done	☐ Yes ☐ No
Blood	☐ Negative	☐ Positive	☐ Normal	☐ Abnormal	☐ Not done	☐ Yes ☐ No

RESEARCH SAMPLES

Date drawn (ddmmmyyyy)**:** _____

Test	*Yes*	*No*	*Comments*
HSV Antibody Titer	☐	☐	
LTA, Elispot-blood	☐	☐	
IFN Gamma Assay	☐	☐	
Blood for future research	☐	☐	

I am confident that the information supplied in this case record form is complete and accurate data. I confirm that the Month 9 Study Visit was conducted in accordance with the protocol and any protocol amendments and that written informed consent was obtained prior to the start of the study procedures.

_____ _____

PI or Co-PI Signature Date (ddmmmyyyy)

C134	Month 12 (± 12 days)	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

MONTH 12 (± 12 days) **Date:** _____
ddmmmyyyy

MRI
Date of procedure (ddmmmyyyy): _____
Was MRI completed? ☐ Yes ☐No
If no, why? _____

ADVERSE EVENTS
Has the subject experienced any adverse events since last visit? ☐Yes ☐ No
Record all Adverse Events on Adverse Event CRF

MEDICATIONS
Have there been any changes to medications? ☐ Yes ☐ No
Record all medication on Concomitant Medications CRF

VITAL SIGNS
Weight (kg): _____._____
Blood Pressure: _____/_____ Heart Rate: _____ bpm
Respiratory Rate: _____ Temperature: _____._____ °C

PHYSICAL EXAMINATION				
System	***Normal***	***Abnormal***	***Not Done***	***Describe if abnormal or give reason not completed***
General Appearance	☐	☐	☐	
HEENT	☐	☐	☐	
Cardiovascular	☐	☐	☐	
Pulmonary	☐	☐	☐	
Abdomen	☐	☐	☐	
Musculoskeletal	☐	☐	☐	
Extremities	☐	☐	☐	
Lymph Nodes	☐	☐	☐	
Dermatology	☐	☐	☐	
Other, Specify _____	☐	☐	☐	

C134	Month 12 (± 12 days)	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

COMPLETE NEUROLOGICAL EXAM			
Level of Consciousness:	☐ Alert	☐Sleepy, but easily aroused	☐Somnolent/difficult to arouse ☐Not arousable
Orientation:	Oriented to time: ☐Yes ☐ No Oriented to place: ☐Yes ☐ No Oriented to self, person and others: ☐Yes ☐ No		
Muscle Strength: (enter corresponding number)	0 = None 1 = Trace 2 = Gravity eliminated 3 = Against gravity 4 = Against resistance 5 = Normal	Right Arm: _____ Left Arm: _____	Right Leg: _____ Left Leg: _____
Gait Evaluation:	☐ Normal ☐ Mildly ataxic ☐ Requires a cane	☐Non-ambulatory	☐Unable to evaluate
Cranial Nerves: Are any cranial nerves affected?	☐ Yes	Left: II III IV V VI VII VIII IX X XI XII Right: II III IV V VI VII VIII IX X XI XII	☐ No
Sensory Exam: Are there abnormalities present? (performed as relevant to tumor location/signs/ symptoms)	☐ Yes_____ ☐ No		
Other Neurological Findings:			
Comments:			

KARNOFSKY PERFORMANCE SCALE	
Percent	***Description***
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 to do active work.
60	Requires occasional assistance, but is able to care for most of his/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.
0	Dead.
Karnofsky Performance Scale: _____%	

C134	Month 12 (± 12 days)	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

LABORATORY ANALYSIS

CBC with diff, plts **Date drawn** (ddmmmyyyy)**:** _____

Test	*Results*		*Clinically Significant*
• Red blood cell count (RBC) o M: 4.40 – 5.80 x 10^6/cmm o F: 3.80 – 5.20 x 10^6/cmm	_____ x 10^6/cmm	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Hemoglobin (Hgb) o M: 13.5 – 17.0 g/dL o F: 11.3 – 15.2 g/dL	_____ g/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Hematocrit (Hct) o M: 39 – 50% o F: 33 – 45%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Platelet count (PLT) o 150- 400 x 10^3/cmm	_____ x 10^3/cmm	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• White blood cell count (WBC) o 4.0 – 11.0 x 10^3/cmm	_____ x 10^3/cmm	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Neutrophils • 35 – 73%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Lymphocytes o 15 – 52%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Monocytes o 4 – 13%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Basophils o 0 – 2%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
▪ Eosinophils o 0 – 5%	_____%	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Mean corpuscular haemoglobin (MCH) o 27 – 33 pg	_____ pg	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Mean corpuscular haemoglobin concentration (MCHC) o 32 – 36 g/dL	_____ g/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Mean corpuscular volume (MCV) o 80 – 96 fL	_____ fL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No

C134	Month 12 (± 12 days)	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

LABORATORY ANALYSIS

Serum Chemistry **Date drawn** (ddmmmyyyy)**:**

Test	*Results*		*Clinically Significant*
• Sodium (Na) o 133 – 145 mEq/L	_____ mEq/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Potassium (K) o 3.1 – 5.1 mEq/L	_____ mEq/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Chloride (Cl) o 97 – 108 mEq/L	_____ mEq/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Bicarbonate (CO_2) o 22 – 32 mEq/L	_____ mEq/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Glucose o 70 – 100 mg/dL (fasting) o 70 – 200 mg/dL (non-fasting)	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Blood urea nitrogen (BUN) o 5 – 22 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Creatinine o M: 0.7 – 1.3 mg/dL o F: 0.4 – 1.2 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Calcium (Ca) o 8.4 – 10.2 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Phosphorus o 2.4 – 5.0 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Total protein o 6.0 – 8.3 g/dL	_____ g/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Uric acid o M: 3.9 – 8.1 mg/dL o F: 2.0 – 6.9 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Gamma-glutamyl transferase (GGT) o 0 – 65 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Aspartate aminotransferase (AST) o 12 – 39 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Alanine aminotransferase (ALT) o 7 - 52 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Creatine kinase (CK) o M: 35 – 250 Units/L o F: 25 – 190 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No

C134	Month 12 (± 12 days)	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

LABORATORY ANALYSIS

Serum Chemistry (cont.)

Test	*Results*		*Clinically Significant*
• Lactate dehydrogenase (LDH) o 120 – 240 Units/L	_____ IU/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Alkaline phosphatase (Alk Phos) o 39 – 117 Units/L	_____ Units/L	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Total bilirubin o 0.3 – 1.4 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Cholesterol (Chol) o 100 – 200 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Triglycerides (TG) o 40 – 150 mg/dL	_____ mg/dL	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Prothrombin time/INR (PT/INR) o 12.0 - 14.5 seconds	_____ seconds	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No
• Partial thromboplastin time (PTT) o 25.0 – 35.0 seconds	_____ seconds	☐ Normal ☐ Abnormal ☐ Not done	☐ Yes ☐ No

LABORATORY ANALYSIS

HSV Detection **Date collected** (ddmmmyyyy)**:**

Test	*Results*					*Clinically Significant*
Saliva	☐ Negative	☐ Positive	☐ Normal	☐ Abnormal	☐ Not done	☐ Yes ☐ No
Conjunctival	☐ Negative	☐ Positive	☐ Normal	☐ Abnormal	☐ Not done	☐ Yes ☐ No
Blood	☐ Negative	☐ Positive	☐ Normal	☐ Abnormal	☐ Not done	☐ Yes ☐ No

RESEARCH SAMPLES

Date drawn (ddmmmyyyy): _____

Test	*Yes*	*No*	*Comments*
HSV Antibody Titer	☐	☐	
LTA, Elispot-blood	☐	☐	
IFN Gamma Assay	☐	☐	
Blood for future research	☐	☐	

I am confident that the information supplied in this case record form is complete and accurate data. I confirm that the Month 12 Study Visit was conducted in accordance with the protocol and any protocol amendments and that written informed consent was obtained prior to the start of the study procedures.

_____ _____

PI or Co-PI Signature Date (ddmmmyyyy)

STUDY TERMINATION **Date:** _____
(ddmmmyyyy)

Did the subject complete the study? ☐ No, check all reasons below ☐ Yes

1. ☐ Adverse Events Date of event: _____
(ddmmmyyyy)
2. ☐ Death Date of event: _____
(ddmmmyyyy)
3. ☐ Lost to Follow-up
4. ☐ Administrative reason, specify: _____
5. ☐ Protocol violation/deviation, specify: _____
6. ☐ Patient noncompliance (refusal or inability to adhere to study requirements)
7. ☐ Sponsor terminated the study
8. ☐ Disease Progression
9. ☐ Other, specify: _____

Specify the code number for the primary reason for termination: _____

I have carefully examined all Case Report Forms for this subject and certify that all of the information entered on the case report forms are, to the best of my knowledge, correct and complete.

_____ _____
PI or Co-PI Signature Date (ddmmmyyyy)

SURVIVAL FOLLOW-UP

Patient status as of: _____
(ddmmmyyyy)

☐ Alive

☐ Dead: Date of death: _____
(ddmmmyyyy)

If Dead, please specify cause of Death: _____

☐ Lost to follow-up: Date last known alive: _____
(ddmmmyyyy)

Is disease progression observed? ☐ Yes ☐ No

If Yes, date of progression: _____
(ddmmmyyyy)

_____ _____

Signature of Person Completing Follow-up Date (ddmmmyyyy)

C134	SURVIVAL FOLLOW-UP	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

Patient status as of: _____
(ddmmmyyyy)

☐ Alive

☐ Dead: Date of death: _____
(ddmmmyyyy)

If Dead, please specify cause of Death: _____

☐ Lost to follow-up: Date last known alive: _____
(ddmmmyyyy)

Is disease progression observed? ☐ Yes ☐ No

If Yes, date of progression: _____
(ddmmmyyyy)

C134	Adverse Event Log	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

☐Check if none

AE #	Adverse Event	Present Pre-C134	Onset Date dd/mmm/yyyy	Resolution Date dd/mmm/yyyy	Grade/Severity	Serious	Relationship to study drug	Frequency	Action taken	Outcome	SAE?
		☐ Yes ☐ No									☐ Yes ☐ No
		☐ Yes ☐ No									☐ Yes ☐ No
		☐ Yes ☐ No									☐ Yes ☐ No
		☐ Yes ☐ No									☐ Yes ☐ No
		☐ Yes ☐ No									☐ Yes ☐ No
		☐ Yes ☐ No									☐ Yes ☐ No
		☐ Yes ☐ No									☐ Yes ☐ No
		☐ Yes ☐ No									☐ Yes ☐ No
		☐ Yes ☐ No									☐ Yes ☐ No
		☐ Yes ☐ No									☐ Yes ☐ No
		☐ Yes ☐ No									☐ Yes ☐ No
		☐ Yes ☐ No									☐ Yes ☐ No
		☐ Yes ☐ No									☐ Yes ☐ No
					1 = Mild 2 = Moderate 3 = Severe 4 = Life-threatening 5 = N/A	1 = Fatal 2 = Life-threatening 3 = Significant disability 4 = Persistent or requires or prolongs hospitalization 5 = Congenital anomaly 6 = Requires medical or surgical interventions 7 = Not serious	1 = Definitely 2 = Probably 3 = Possibly 4 = Unlikely 5 = Not related	1 = Single 2 = Continuous 3 = Intermittent	1 = None 2 = Study drug discontinued 3 = Dose adjusted 4 = Study drug stopped/restarted 5 = Treatment required 6 = Hospitalization or prolongation of 7 = Other	1 = Ongoing 2= Grade change 3 = Resolved 4 = Death 5 = Unk/Lost to follow-up	

I have carefully examined all Adverse Events for this subject and certify that all of the information entered above are, to the best of my knowledge, correct and complete.

______________________________ ______________________

PI or Co-PI Signature **Date (dd/mmm/yyyy)**

C134	Concomitant Medications	Subject Initials: ___ ___ ___	Subject Number: ___ ___ ___

☐ **Check if none**

Record generic name except for combination drug products where brand name can be recorded. Record date medication is started and stopped for each change in dose, route, frequency or indication.

Medication	Start Date dd/mmm/yyyy	Stop Date dd/mmm/yyyy	Dose (mg, g, ml, etc.)	Route 1 = PO 2 = IV 3 = IM 4 = SQ 5 = Other	Frequency 1 = QD 2 = BID 3 = TID 4 = QID 5 = PRN 6 = Every ___ hrs	Indication	AE# (if applicable)	Ongoing
								☐
								☐
								☐
								☐
								☐
								☐
								☐
								☐
								☐
								☐
								☐

I have carefully examined all Concomitant Medications for this subject and certify that all of the information entered above are, to the best of my knowledge, correct and complete.

PI or Co-PI Signature **Date (dd/mmm/yyyy)**

DEATH REPORT

Date of report: _____
(ddmmmyyyy)

Date of Death: _____
(ddmmmyyyy)

Primary cause of death: _____
Please report on Adverse Event and Serious Adverse Event CRF's

Relationship of Death to C134 (check one):

☐ Not related ☐ Unlikely ☐ Possibly related ☐ Probably related ☐ Definitely related

Relationship of Death to Disease (check one):

☐ Not related ☐ Unlikely ☐ Possibly related ☐ Probably related ☐ Definitely related

Autopsy Performed? ☐ No ☐ Yes If YES, attach a copy of autopsy report

Is autopsy report attached? ☐ No ☐ Yes

I am confident that the information supplied in this death report form is complete and accurate data.

_____ _____
PI or Co-PI Signature Date (ddmmmyyyy)

MACDONALD RESPONSE CRITERIA

Date of Assessment (ddmmmyyyy): _____ Visit: _____ MRN: _____

Measurements: _____ mm X _____ mm

Location of tumor	Right	Left
Frontal		
Parietal		
Occipital		
Temporal		
Cerebellum		
Brainstem		
Corpus Callosum		
Lateral Ventricle		
3rd or 4th Ventricle		
Basal ganglia or thalamus		
Other, specify:		

"Response" is defined as follows:

□ Complete Response (CR)	Disappearance of all treated enhancing tumor on MRI scan, off steroids, and neurologically stable or improved.
□ Partial Response (PR)	Greater than 50% reduction in the treated enhancing tumor on MRI scan, stable or reduced steroid dose, and neurologically stable or improved.
□ Progressive Disease (PD)	Greater than 25% increase in the treated enhancing tumor on MRI scan, stable or increased steroid dose, and neurologically stable or worse.
□ Stable Disease (SD)	All other situations.

INFORMED CONSENT

Title of Research:	A Phase I Trial of IRS-1 HSV C134 Administered Intratumorally in Patients with Recurrent Malignant Glioma.
UAB IRB Protocol #:	IRB-300000571
Principal Investigator:	James Markert, M.D.; L. Burton Nabors, M.D.
Sponsor:	The Gateway for Cancer Research National Institutes of Health (NIH)

Purpose of the Research

You have been asked to participate in this research study because you have a malignant brain tumor that has not responded to standard treatment. This document will tell you about the purpose, risks, and benefits of this study. You should provide your consent only after you have received all the necessary information and have had enough time to decide whether you wish to participate. Please feel free to ask any questions before you agree to take part in this study.

The purpose of this study is to determine how safe and how well-tolerated the experimental study drug, C134 is when administered into the brain where the tumor is located. This is a Phase I study and is being conducted by Dr. James Markert at the University of Alabama at Birmingham. The purpose of a Phase I study is to establish a safe dose range based on side effects of the study drug being tested, in this case, C134. All the patients who take part in this study will receive the same type of experimental treatment, although some people will receive higher doses than other people. There is no “placebo” in this study. Varying doses of C134 will be administered in this study and the dose you receive will be determined by the number of participants given the drug before you and their response to the medication. Anywhere from 4 to 24 patients are expected to take part in the study; the final number will depend on the safety results.

Background

C134 is a genetically engineered herpes simplex virus or "HSV" (the virus that usually causes cold sores and rarely, a severe infection of the brain). It has been known that viruses may kill tumor cells. When tumor cells are mixed with certain viruses in the laboratory, the tumor cells die. The DNA of the (HSV) virus has been modified so that tumor cells may be killed when infected by C134. The changes made to the virus (HSV) should help prevent the (C134) virus from infecting normal brain tissue. Extensive testing in both mice and monkeys has demonstrated that C134 is not able to cause HSV when injected directly into the brain. C134 may also be able to help kill tumor cells because it can prevent tumor cells from killing it more effectively than other, similar viruses can. This allows it to infect and kill more brain tumor cells. More than 40 patients with malignant brain tumors have been treated by injecting an earlier

version of this HSV virus into their tumors and surrounding brain tissues without producing any serious side effects. Based on laboratory testing, C134 may be more effective against your brain tumor than the earlier virus.

Explanation of Procedures

This study is divided into the following sections, also called phases: the Screening Phase, the Treatment Phase and the Follow-up Phase. Before you can participate in the study, tests will be performed to make sure that you qualify for the study. This is called the Screening Phase. If you qualify for the study you will then enter the Treatment Phase which is the phase where you receive the study drug and then enter the Follow-up Phase.

Screening Phase (approximately 2 weeks prior to Treatment Phase):

The total length of this visit will be approximately 2-4 hours. If you agree to participate in the study, you will come in for a screening visit. The following will take place during this visit:

- Informed consent will be signed before any study-related procedures are performed.
- You will be asked questions about your medical history, medications you are taking, and how you feel.
- You will have a complete physical examination, and your pulse, blood pressure, respiratory rate, temperature, height and weight will be checked. All exams and data are being collected for research purposes.
- You will have a neurological (nervous system) examination for research purposes to check your general nervous system function and muscle strength.
- Routine lab tests will be performed to confirm that it is safe for you to undergo surgery.
- A blood sample will be collected for research purposes and tested to evaluate the general state of your health, look at your immunity (including HIV status) and test for the presence of the herpes virus. Special research blood tests to monitor the body's ability to send signals to the immune system to target the tumor will also be done; these will include a special genetic test done on white blood cells. This testing will tell investigators what kind of immune responses against the tumor might be present before C134 treatment.
- The blood samples will be obtained by inserting a needle into a vein in your arm (venipuncture). The blood tests will require that approximately 10 teaspoons of blood be drawn, a total of approximately 1 cup over the course of this study.
- Samples of conjunctival (eye) secretions will be collected by gently touching separate sterile cotton tipped swabs to the corner of each eye. This test is done for research purposes and will test for the presence of the herpes virus, to see if you have any herpes simplex virus in your saliva. This will determine if any HSV was present in your eye secretions before C134 was given.
- Saliva will be collected by placing one sterile cotton tipped swab into the mouth. This test is done for research purposes and will test for the presence of the herpes virus, to

see if you have any herpes simplex virus in your saliva. This will determine if any HSV was present in your saliva before C134 was given.

- A routine urine pregnancy test for women capable of bearing children will be collected. All women will have additional urine pregnancy tests during the study, if needed. In addition, men and women must have been using an effective method of birth control before receiving the study drug. You must also agree to continue to use "barrier" birth control (condoms) during the study and for six (6) months following the administration of the study drug.
- An electrocardiogram (ECG) will be performed for research purposes to check the electrical activity of your heart.
- A routine chest x-ray will be performed to check for any signs of infection at baseline. The data from the chest x-ray will be evaluated for research.
- Brief Quality of Life assessment will be made for research purposes. This Brief Quality of Life assessment consists of 2 surveys (Herth Hope Index and MD Anderson Symptom Inventory-Brain Tumor) and a physician assessment (Karnofsy Performance Scale) will be made for research purposes. These 3 assessments are hereafter collectively referred to as Quality of Life or QoL assessment.

Treatment Phase:

The total length of this phase (Day 0-Day 3) will be approximately 4 days. If the results of the screening visit indicate you are eligible, you will be enrolled into the study. You will be hospitalized for a total of approximately 4 days. The first night in the hospital is routine care and the additional days are research related. As part of this research study, you will have the surgical procedure described in the Study Procedures section below to place the small tube called a “catheter” into various parts of the tumor, and the drug, C134, will be injected into the brain tumor. The catheter is slightly larger than a pencil lead and will be used to deliver C134 into various regions of the tumor and then will be removed and the surgical wound will be closed with sutures. The total time required to inject the tumor is expected to be 90-120 minutes. Following the surgery, you will be monitored closely in the Neuro-Intensive Care Unit overnight, and then be transferred to the Neurosurgery unit and/or Clinical Research Unit when your doctor feels you are stable enough. As part of the research study, your temperature, blood pressure, breathing and heart rate ("vital signs") and nervous system checks will be performed frequently after surgery and the administration of C134 to monitor your progress. The nervous system checks may include all or some of the following: walking, measures of alertness, muscle strength and any changes in movement. You will be discharged when your doctor feels you are stable enough to leave the hospital.

Day 0 (biopsy and catheter placement)

- If able, an ophthalmologic evaluation may be performed. This is an optional evaluation and should not delay your treatment
- You will be admitted to the hospital, as routine care, for biopsy surgery and if eligible, catheter placement for research purposes.

- You will be asked questions about medications you are currently taking and any changes to your health since last visit.
- Vital signs (pulse, blood pressure, respiratory rate and temperature) will be obtained prior to surgery.
- You will have a neurological (nervous system) examination for research purposes to check your general nervous system function and muscle strength.
- An additional research-only MRI may be performed to determine exact location of the tumor for the biopsy and catheter placement if the surgeon determines it to be necessary.
- As part of routine care, you will also be given medication into a vein (intravenous) to help you relax and feel sleepy before the procedure. You will also receive medication to minimize any pain (local anesthesia) before the surgery.
- The research surgical procedure is called stereotactic (stereo-tactic) surgery because of the way all the areas of the brain are identified using the MRI scan and other images and a special delivery system explained below. This surgery involves using a special removable frame that can be connected to the skull with small screws or pins. The frame is used to guide the tubing used for injecting C134 in a precise location so that the study drug can be administered directly into the tumor.
- Before the study drug is injected, as part of routine care, your doctor will take a small sample of tissue (biopsy) to check for tumor cells and confirm the diagnosis of brain cancer. A thin, long needle connected to the stereotactic frame will be guided to the tumor. This procedure is routinely performed in participants for whom a brain biopsy is needed. If the diagnosis of recurrent tumor is confirmed, then the surgical procedure will proceed to prepare for the delivery of the drug.
- The tumor will eventually undergo genetic testing to look for abnormal proteins on the surface of the tumor cells that might allow C134 to cause an antitumor immune response, like a vaccine. Another kind of genetic testing will be done to determine if there are certain subtypes of tumors that respond either better or less well to C134 treatment.
- After verification of tumor recurrence has been confirmed from the biopsy report, the administration of C134 will be done in the operating room.
- You will be assigned to receive one of the five pre-determined doses of C134 through the catheters. The study drug will be injected directly through a needle and tube into your tumor. The catheter will be moved as needed and the virus injected in up to 5 different locations.
- After the surgery, you will be admitted to the Neurosurgery Intensive Care where your vital signs will be monitored frequently and frequent neurological exams will be performed
- Participants should avoid contact with infants and young children, individuals with decreased immunity (ability to fight infection), and pregnant women (including intimate contact). Participants should also refrain from donating blood during the trial.

- Close contacts and family members should refrain from direct physical contact until HSV detection results in a negative shedding.

Day 1 (all evaluations are for research purposes):

- Your medications will be reviewed and updated
- A physical exam will be performed and your wound will be examined.
- Your vital signs will be monitored frequently
- Neurological exams will be performed frequently
- You will be monitored for any signs of adverse events or reactions to the drug
- Samples conjunctival (eye) secretions, blood, and saliva will be collected to see if you have any herpes simplex virus in your eye secretions, blood or saliva after C134 was given.

Day 2 (all evaluations are for research purposes):

- A repeat of evaluations from Day 1
- Samples conjunctival (eye) secretions and saliva will be collected, to see if you have any herpes simplex virus in your eye secretions or saliva. This will determine if any HSV was present in your eye secretions after C134 was given.
- A blood sample will be collected. Special research blood tests, including some genetic tests that monitor the body's ability to send signals to the immune system to target the tumor will also be done. (Acceptable up to Day 4)
- Samples conjunctival (eye) secretions, blood, and saliva will be collected to see if you have any herpes simplex virus in your eye secretions, blood, or saliva after C134 was given.

Day 3 (all evaluations are for research purposes):

- A repeat of evaluations from Day 1.
- An MRI scan will be performed
- You will be discharged if your doctor feels you are stable enough to leave the hospital.
- Samples conjunctival (eye) secretions and saliva will be collected to see if you have any herpes simplex virus in your eye secretions, blood, or saliva after C134 was given.

Follow-up Phase

You will return to the clinic for eight (8) follow-up visits. All of these follow-up visits are due to your involvement in this research study.

In addition to the MRI completed to qualify you for the study, MRIs will also be performed during the first week and then later on day 28, and at three months, six months and twelve months after surgery. The MRIs performed during the first week and on Day 28 are specifically for the study and not considered standard of care. The remaining MRI scans are considered standard of care but will also be used for research purposes in your case. A total of 6-7 MRI scans will be performed on you throughout the study period to monitor your tumor. If there are

signs or symptoms that the tumor has become larger, additional MRIs may be performed if your doctor feels they are necessary for your routine care. It is also possible that your doctor may need to take a biopsy sample of the brain to determine the cause of any increase in signs or symptoms you may be having. If this is the case, your doctor will discuss this with you at the time and explain details of the procedure to you.

Day 7 (± 3 days) - Total length of this visit will be approximately 1 hour

- A ophthalmologic exam will be performed

Day 10 (± 3 days) - Total length of this visit will be approximately 2 hours.

- Your medications will be reviewed and updated
- You will be asked about any changes to your health since your last visit.
- A physical exam will be performed.
- Your vital signs will be monitored
- Neurological exams will be performed
- A blood sample will be collected
- Samples conjunctival (eye) secretions and saliva will be collected to see if you have any herpes simplex virus in your eye secretions or saliva. This will determine if any HSV was present in your eye secretions after C134 was given.
- All activities and exams on Day 10 visit are for research purposes

Day 14 (± 3 days) - Total length of this visit will be approximately 1 hour

- A ophthalmologic exam will be performed

Day 21 (± 3 days) - Total length of this visit will be approximately 1 hour

- A ophthalmologic exam will be performed

Day 28 (± 4 days) - Total length of this visit will be approximately 3-4 hours.

- A repeat of evaluations from Day 10
- A research-only MRI scan will be performed
- Brief Quality of Life assessments will be made
- All activities and exams on Day 28 visit are for research purposes.
- Samples conjunctival (eye) secretions, blood and saliva will be collected to see if you have any herpes simplex virus in your eye secretions or saliva. This will determine if any HSV was present in your eye secretions, blood, or saliva after C134 was given.

Months 3, 6, and 12 - Total length of this visit will be approximately 3-4 hours.

- A repeat of evaluations from Day 10
- A routine MRI scan will be performed
- Brief Quality of Life assessments will be made for research purposes.

- Samples conjunctival (eye) secretions, blood, and saliva will be collected to see if you have any herpes simplex virus in your eye secretions or saliva. This will determine if any HSV was present in your eye secretions, blood or saliva after C134 was given.

Risks and Discomforts

Blood Draws

There may be some temporary pain, bruising, bleeding or rarely, infection at the site where blood samples are drawn from your arm. Although rare, some individuals may become faint during blood drawing procedures. These complications are rarely severe.

MRI Scans

Magnetic Resonance Imaging (MRI) scans are a painless imaging procedure and are very safe for most people. Some discomfort may be experienced since you must lie flat and remain as still as possible in a long plastic cylinder for approximately 30-45 minutes. Some people also experience anxiety due to fear of being in close spaces. You will be closely observed at all times and can be assisted, if necessary by the hospital staff performing the procedure. You may be moved out of the machine at your request or, if you are experiencing severe anxiety, you may be given anti-anxiety medication prescribed by your doctor to make you less anxious. If you would like, ear plugs are available to you to decrease the knocking noise you hear that is made by the machine. Pillows will be placed under your knees to make you comfortable and you will be covered with a sheet or blanket to keep you warm, if needed.

For a portion of the MRI, a needle will be placed into your vein (intravenous line or "IV") and dye will be injected into your vein. This dye helps to give a better picture of the brain tumor and surrounding brain.

Participants who are at risk for injury from MRI such as former welders or those with pace makers, aneurysm clips, (metal clips on the wall of a large artery), metal infusion pumps, or metal and/or shrapnel fragments, will not be entered into the study.

Risk of MRI contrast (dyes)

A small number of people may develop brief reactions during administration of the dye used in MRI testing, including nausea, a bad aftertaste, headaches, hot flashes and heart palpitations (heart skipping a beat). A smaller group of participants may also be allergic to the dye and may develop a rash, itching, hives, breathing difficulties, kidney problems, and in extreme cases, death. You will be closely monitored throughout the procedure and if an allergic reaction develops, you will be treated promptly. We are unable to determine the specific MRI contrast drugs that will be utilized, but it is likely that we will use one of the top two agents, gadoteridol and gadoterate meglumine. The risks are particularly uncommon in the two MRI dyes planned for use in the research portion of this study. Other dyes might be used if you have a previous

sensitivity to one of these two dyes. These other dyes generally have a similar side effect profile to the two mentioned; significant differences will be discussed with you prior to the test.

Also, there is a very small risk of nephrogenic systemic fibrosis (NSF) with the dye used for MRIs scans. NSF is an extremely rare condition that has been seen in patients with decreased kidney function who receive the MRI dye (gadolinium). It can cause hardening of the skin, the tissue under the skin, muscle tissue hardening, scarring around internal organs and in very rare occasion, death. Even in the absence of NSF, the dye could cause problems with kidney function or an allergic reaction resulting in a rash, itching, hives, breathing difficulties and in extreme cases, death.

There is also a risk of gadolinium staying in the brain after this dye is given during the MRIs. Currently, there are no known toxic effects of this deposition, but long-term studies have not been reported. The FDA currently does not feel there are safety issues with the gadolinium dyes currently in use.

Surgery/Catheter Placement and Removal

The surgical risks of the stereotactic procedure you will depend on your condition before the surgery and the location and size of your tumor. Risks known to be associated with brain surgery, involving catheter placement include:

- Hemorrhage (bleeding)
- Deterioration of nervous system function such as:
  - weakness in the arm and or leg
  - loss of sensation over parts of your body
  - partial or complete loss of function related to communication, such as speech and comprehension
  - other functions related to intellectual capacity, such as memory
- Infection and death
- Mild Pain or Discomfort (Catheter removal requires placement of a new suture to close the skin and prevent infection and this is usually done while you are under anesthesia. This may cause some mild pain or discomfort. Pain medicine will be available to minimize your discomfort during this portion of the procedure should you wish it.)

The relative risks of these procedures, considering your condition, will be discussed with you by your doctor.

Risks of Herpes Simplex Virus-C134

Herpes simplex virus is the virus that usually causes cold sores and rarely, a severe brain infection. It can also infect other tissues such as skin and the mucous membranes of the mouth, eyes and urinary tract.

This research study will involve the injection of a modified herpes simplex virus into the brain. Based on laboratory studies done in mice and monkeys, the modification should allow the C134 virus to infect and kill tumor cells but not normal brain tissue. This, however, cannot be assured in humans. Of the first 10 participants enrolled in this study, one participant with extremely advanced tumor experienced the modified virus producing widespread inflammation in the brain around the tumor, which altered their mental status and cognition severely and another participant experienced the modified virus moving from the tumor into the eye, which resulted in partial visual loss that was permanent. Mandatory ophthalmologic exams will be performed at Day 7, Day 14, and Day 21 to monitor for any eye issues and treatment will be given as needed. The purpose of this study is to find out which dose of the virus can be given without any toxic effects.

Based on prior studies with related viruses, we do not expect these risks to occur with any significant frequency. However, this is a Phase I study and it is unknown currently whether there will be any increase in risks with escalating dose levels for severity, frequency or reversibility of these risks.

The potential risks of C134 include, but are not limited to:

- Inflammation of the liver (hepatitis) that could cause death (very rarely)
- Wide-spread viral infection with effects ranging from flu-like symptom to more severe reactions
- Allergic reaction to the virus causing symptoms ranging from itching and hives to severe cases, difficulty breathing.
- Infection of the brain (encephalitis), which may cause high fevers, confusion, loss of consciousness
- Neurologic difficulties, seizures and even death

The virus in this study has been modified to prevent the development of infection of normal brain cells. However, if you should develop an infection of the brain, you will be treated with the standard medical therapy that is very effective in treating and eliminating this kind of infection. This therapy to destroy the virus uses medications to fight the virus (anti-viral drugs). Should this anti-viral therapy be needed, it would require that you be hospitalized and receive daily intravenous infusion of the anti-viral drug acyclovir or similar drug for 14-21 days. With early treatment, anti-viral drugs like acyclovir and others are likely to halt progression of herpes simplex viral infection. Your doctor may need to perform tests to help determine if there is such an infection. These might include a biopsy of brain tissue or testing of the fluid surrounding the spinal cord and the brain called cerebrospinal fluid (CSF).

Your doctor will discuss these procedures with you if it becomes necessary to perform them. The risks of a brain biopsy include the possibility of bleeding, infection or low grade fever, and in rare cases, deterioration in nervous system functioning. If a sample of CSF is needed, a small needle will be placed in the small of the back into the space around the spinal cord (lumbar

puncture) and a sample of fluid removed. This can result in headache and in rare cases, worsening of nervous system functioning.

There is also a risk that the tumor itself may swell as a result of virus injection, causing headache, lethargy (sleepiness and tiredness), nausea, vomiting, seizures, neurological deficits or even death. Should tumor swelling develop, you will receive treatment with steroids (drugs that decrease inflammation and swelling) for as long as it is necessary. If nervous system deficits persist despite steroid treatment, there is a chance that your doctor would recommend surgery to remove some or all of the swollen tumor and ease the pressure on the surrounding brain.

You will be monitored closely throughout the trial for signs and symptoms of infection so that you can be treated promptly.

Most people in the United States have already been exposed to herpes simplex virus and have antibodies against the virus. If you do not have antibodies against the virus, it is possible that you will develop them after receiving C134. These antibodies help fight infection from the herpes simplex virus and are not harmful.

Based upon the risks of brain biopsy, we know that rarely-occasionally (from 0-20 out of 100 patients), a significant episode of bleeding into the brain, infection or low grade fever, seizure, or neurologic problem can occur, sometimes serious.

Since C134 has not been used in people before, it is impossible to estimate the rate of side effects from it and these are really unknown. However, based upon results from prior studies with other viruses, we estimate that the risks of headaches, lethargy, nausea, vomiting, seizures and mild and temporary neurologic deficits including possible problems with speech, weakness, vision or numbness after C134 administration may occur occasionally (between 4 and 20 people out of 100). Rarely, these could be serious enough to warrant an increase in the duration of hospitalization or a new hospitalization. We estimate the risk of brain infection (encephalitis), liver inflammation (hepatitis), severe allergic reaction, and widespread viral infection or death to be rare and severe permanent neurologic problems to be rare (fewer than 3 out of 100 people treated).

Seizure medications (Anticonvulsants)
Because there may be an increased risk of seizures after C134 administration, for about one month during and after patients will be placed on an anti-seizure medication (or a second anti-seizure medication if they are already on one). Since the anti-seizure drug to be added will be individualized per patient history, allergies, other medications, etc., no obvious prediction can be made of which drug might be utilized-for this reason. Common risks of frequently used seizure medications include sleepiness/fatigue, insomnia, dizziness, personality changes, double or blurred vision, tingling sensations, tremors balance or memory problems; nausea, vomiting, diarrhea, liver problems, or other GI problems; infection or influenza; headache or pain, ,

decreased blood counts; birth defects; and mild allergic reactions like cough, rash or itching. Rare risks include severe allergic reactions leading to blood pressure or breathing problems or even death, or suicide. Should you be concerned about any side effects of a seizure medication, please discuss these with your doctor so another medication may be substituted as quickly as possible. At that time, your doctor can discuss any significant differences in side effect risks of the new medicine with you.

Risk of Immune Activity in the Brain
The risk of C134 therapy in the brain is unknown, but could potentially include permanent damage to neurologic function due to swelling or even the development of an autoimmune response in which the body's infection fighting cells perceive normal brain as infection and attack it. This could potentially produce problems similar to Multiple Sclerosis (MS). Other, unknown effects could also occur including but not limited to stroke, bleeding, dangerously low blood pressure, damage to liver or kidney function, or even death.

Data Safety/Confidentiality Breach
Information obtained about you for this study will be kept confidential to the extent allowed by law. However, research information that identifies you may be shared with the UAB Institutional Review Board (IRB) and others who are responsible for ensuring compliance with laws and regulations related to research, including the Office for Human Research Protections (OHRP). The information from the research may be published for scientific purposes; however, your identity will not be given out.

If you are a patient, and if any part of this study takes place at University of Alabama Hospital, this consent document may be placed in your file at that facility. The document may become part of your medical record chart. Further, information relating to this study, including your name, medical record number, date of birth and social security number, may be shared with the billing offices of UAB and UAB Health System affiliated entities so that the costs for clinical services can be appropriately paid for by either the study account or by the patient/patient's insurance.

A federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and some employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware that this new federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance, nor does it protect you against genetic discrimination by all employers.

All specimens are coded and stored in freezers in locked laboratories with limited access. All data is coded in a password- and firewall-protected database kept in a secure office. You or a member of your family may still voluntarily release information about yourself or your involvement in this research.

Unknown Risks
C134 administration into tumor is new and it is possible that despite our extensive efforts, unforeseen problems may occur including the possibility of unknown and possible disabling effects or death.

Information for Women of Childbearing Potential, Nursing Mothers, and/or Men Capable of Fathering a Child
We do not know if the study drug will affect mother's milk or an unborn fetus. Therefore, breast-feeding and pregnant women are not allowed to take part in the study. If you are pregnant or become pregnant, there may be risks to the embryo or fetus that are unknown at this time. Women who can become pregnant must take a pregnancy test before the start of the study.

You should not father a child while on this study as the treatment may indirectly affect an unborn child. If you are sexually active and are at risk of causing a pregnancy, you and your female partner(s) must use a birth control method to avoid pregnancy that works well or you must not have sex.

Unless you cannot have children because of surgery or other medical reasons, you must have been using an effective form of birth control before you start the study. Because it is currently unknown if C134 can be transmitted by sexual contact, you must also agree to continue to use an effective form of barrier birth control for 6 months after taking the study drug. Effective barrier birth control includes condoms and abstinence.

Benefits
There may be no direct benefit to you from this study. While it is also possible that this experimental treatment may kill some of your tumor cells, there may still be no beneficial effect on the course of your illness. Because of your participation in this study, we may learn more about potential ways to treat brain tumors. This information may prove useful in the future treatment of patients with brain tumors.

Alternatives

You are being offered the opportunity to participate in this study after your tumor recurred, despite appropriate standard therapies for your disease. Other therapy options have been explained to you, including:

- Gliadel®, a wafer that releases a chemotherapy agent that is implanted into the area of the brain tumor
- Radiation therapy to the brain
- Additional surgery, to remove tumor
- Other Chemotherapy

There are no other standard treatments that have been shown to have significant effects in patients with your disease. A variety of experimental studies for the treatment of brain tumors are conducted in medical centers around the world, but the benefit of their approaches is yet unknown. In addition, you may decline any further treatment for your disease.

If at any time after receiving C134, there are signs or symptoms indicating growth of the tumor, your doctor will again discuss alternative therapies that may be of benefit to you. If you are treated with alternative therapies after receiving C134, you will still be permitted to continue on the study and be monitored for effects of C134.

Confidentiality

Information obtained about you for this study will be kept confidential to the extent allowed by law. However, research information that identifies you, such as your date of birth and initials, may be shared with people or organizations for quality assurance or data analysis, or with those responsible for ensuring compliance with laws and regulations related to research. They include:

- UAB Institutional Review Board (IRB). An IRB is a group that reviews the study to protect the rights and welfare of research participants.
- The Gateway for Cancer Research, funding agency for this trial
- National Institutes of Health (NIH), funding agency for this trial
- Food and Drug Administration (FDA)
- Office for Human Research Protections (OHRP)
- UAB Comprehensive Cancer Center
- Data Safety and Monitoring Board for this study

The information from the research may be published for scientific purposes; however, your identity will not be given out.

Your consent form will be placed in your medical record at UAB Health System. This may include either a paper medical record or electronic medical record (EMR). An EMR is an electronic version of a paper medical record of your care within this health system. Your EMR may indicate that you are on a clinical trial and provide the name and contact information for the principal investigator.

If you are receiving care or have received care within this health system (outpatient or inpatient) and are participating in a research study, results of research tests or procedures (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in your existing medical record.

If you have never received care within this health system (outpatient or inpatient) and are participating in a research study, a medical record will be created for you to maintain results of research tests or procedures.

All information within your medical record can be viewed by individuals authorized to access the record.

If you have questions about clinical trial billing at a UAB Health System location, contact the Office of Clinical Billing Review at fap@uab.edu. For more on UAB's Fiscal Approval Process requirements, go to FAP - Site Minder Processes that can be located online at http://www.uab.edu/research/administration/offices/CBR/Pages/Processes.aspx.

Information relating to this study, including your name, medical record number, date of birth and social security number, may be shared with the billing offices of UAB and UAB Health System affiliated entities, so that the costs for clinical services can be appropriately paid for by either the study account or by your insurance.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Voluntary Participation and Withdrawal

Whether or not you take part in this study is your choice. There will be no penalty if you decide not to be in the study. If you decide not to be in the study, you will not lose any benefits you are otherwise owed.

You are free to withdraw from this research study at any time. Your choice to leave the study will not affect your relationship with this institution. You should return to see the study doctor for safety reasons so you can be taken off the study drug and referred for follow-up care.

If you end the study early, you will be asked to have blood tests and the same physical and nervous system exams you previously had. It is also possible your doctor will request an MRI at this time.

You may be removed from the study without your consent if the sponsor ends the study, if the study drug is approved by the FDA, if the study doctor decides it is not in the best interest of your health, or if you are not following the study rules.

Cost of Participation in Research

There will be no cost to you for taking part in the research portion of this study. All drugs (for example C134, additional anti-seizure medication) exams (for example, the MRI Day 3 and Day 28), hospital Day 2 and Day 3 and medical care related to this study will be provided to you at no cost during the 12 month study period.

The costs of your standard medical care which relate to the biopsy, including the biopsy itself and first night of hospitalization, as well the MRI scans that would be obtained whether or not you were in the trial (screening, Biopsy/Day 0 and Day 1, Month 3, Month 6 and Month 12) and other similar expenses (pain medications, physical therapy, etc.) will be billed to you and/or your insurance company in the usual manner.

If you are in Medicare Advantage (Medicare managed care plan), you should contact someone at your plan before you start a clinical trial. They can provide more information about additional costs you could incur from participating in clinical trials.

Payment for Participation in Research

No compensation is available for taking part in this research study.

Payment for Research Related Injuries

UAB, Gateway for Cancer Research, and NIH have not provided for any payment if you are harmed as a result of taking part in this study. If such harm occurs, treatment will be provided. However, this treatment will not be provided free of charge.

Significant New Findings

Any significant new findings that develop during the course of the study, which may affect your willingness to continue in the research, will be provided to you by Dr. James Markert or his staff.

Optional Studies

As part of this study, we would like to store some of the blood and tissue specimens collected from you for future research on malignant glioma. The future research may be conducted by the study doctor or by other researchers that obtain IRB approval for their research. The specimens will be labeled with a code that only the study doctor can link back to you. Results of any future research will not be given to you or your doctor. The specimens obtained from you in this research may help in the development of a future commercial product. There are no plans to provide financial compensation to you should this occur. You do not have to agree to allow your specimens to be stored in order to be part of this study.

You may request at any time that your specimens be removed from storage and not be used for future research. If you decide you want your specimens removed, you may contact the study doctor. Once the request is received, and if your specimens have not already been used for other research, they will be destroyed. If you do not make such a request, your specimens will be stored indefinitely or until used.

Initial your choice below:

___ I agree to allow my specimens to be kept and used for future research on malignant glioma.

___ I do not agree to allow my specimens to be kept and used for future research.

Questions

If you have any questions, concerns, or complaints about the research or a research-related injury including available treatments, please contact the study doctor. You may contact Dr. James M. Markert at 205-996-2461 or after hours by paging him at 205-934-3411 (pager 5562).

OR

You may also call Dr. Burt Nabors at 205-934-1432. He may also be reached after hours calling the Department of Neurology, Division of Neuro-oncology after hour service number 205-934-3411

If you have questions about your rights as a research participant, or concerns or complaints about the research, you may contact the UAB Office of the IRB (OIRB) at (205) 934-3789 or toll free at 1-855-860-3789. Regular hours for the OIRB are 8:00 a.m. to 5:00 p.m. CT, Monday through Friday.

Legal Rights

You are not waiving any of your legal rights by signing this consent form.

Signatures

Your signature below indicates that you agree to participate in this study. You will receive a copy of this informed consent.

Signature of Participant or Legally Authorized Representative Date

Signature of Person Obtaining Consent Date

University of Alabama at Birmingham
AUTHORIZATION FOR USE/DISCLOSURE OF
PROTECTED HEALTH INFORMATION (PHI) FOR RESEARCH

Participant Name: _____ **UAB IRB Protocol Number:** IRB-300000571
Research Protocol: A Phase I Trial of IRS-1 HSV C134 Administered Intratumorally in Patients with Recurrent Malignant Glioma **Principal Investigator:** James M. Markert, MD
Sponsor: Gateway for Cancer Research, NIH

What is the purpose of this form? You are being asked to sign this form so that UAB may use and release your protected health information for research. Participation in research is voluntary. If you choose to participate in the research, you must sign this form so that your protected health information may be used for the research.

Why do the researchers want my protected health information? The researchers want to use your protected health information as part of the research protocol listed above and as described to you in the informed consent.

What protected health information do the researchers want to use? All medical information, including but not limited to information and/or records of any diagnosis or treatment of disease or condition, which may include sexually transmitted diseases (e.g., HIV, etc.) or communicable diseases, drug/alcohol dependency, etc.; all personal identifiers, including but not limited to your name, social security number, medical record number, date of birth, dates of service, etc.; any past, present, and future history, examinations, laboratory results, imaging studies and reports and treatments of whatever kind, including but not limited to drug/alcohol treatment, psychiatric/psychological treatment; financial/billing information, including but not limited to copies of your medical bills, and any other information related to or collected for use in the research protocol, regardless of whether the information was collected for research or non-research (e.g., treatment) purposes.

Who will disclose, use and/or receive my protected health information? All Individuals/entities listed in the informed consent documents, including but not limited to, the physicians, nurses and staff and others performing services related to the research (whether at UAB or elsewhere); other operating units of UAB, HSF, UAB Highlands, Children's of Alabama, Eye Foundation Hospital, and the Jefferson County Department of Health, as necessary for their operations; the IRB and its staff; the sponsor of the research and its employees and agents, including any CRO; and any outside regulatory agencies, such as the Food and Drug Administration, providing oversight or performing other legal and/or regulatory functions for which access to participant information is required.

How will my protected health information be protected once it is given to others? Your protected health information that is given to the study sponsor will remain private to the extent possible, even though the study sponsor is not required to follow the federal privacy laws. However, once your information is given to other organizations that are not required to follow federal privacy laws, we cannot assure that the information will remain protected.

How long will this Authorization last? Your authorization for the uses and disclosures described in this Authorization does not have an expiration date.

Can I cancel this Authorization? You may cancel this Authorization at any time by notifying the Principal Investigator, in writing, referencing the research protocol and IRB Protocol Number. If you cancel this Authorization, the study doctor and staff will not use any new health information for research. However, researchers may continue to use the protected health information that was provided before you cancelled your authorization.

Can I see my protected health information? You have a right to request to see your protected health information. However, to ensure the scientific integrity of the research, you will not be able to review the research information until after the research protocol has been completed.

Signature of participant: _____ Date: _____
or participant's legally authorized representative: _____ Date: _____
Printed Name of participant's representative: _____
Relationship to the participant: _____