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A Pilot Study and Phase II Double Blind Placebo Controlled Randomized Trial Examining the Safety and Efficacy of Glyburide as Prophylaxis Against Cerebral Edema in Patients Receiving Radiosurgery for Brain Metastases

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Protocol Agents

Agent	**Supply**	**NSC #**	**IND #**
Non-Micronized Glyburide	Commercial	N/A	Exempt

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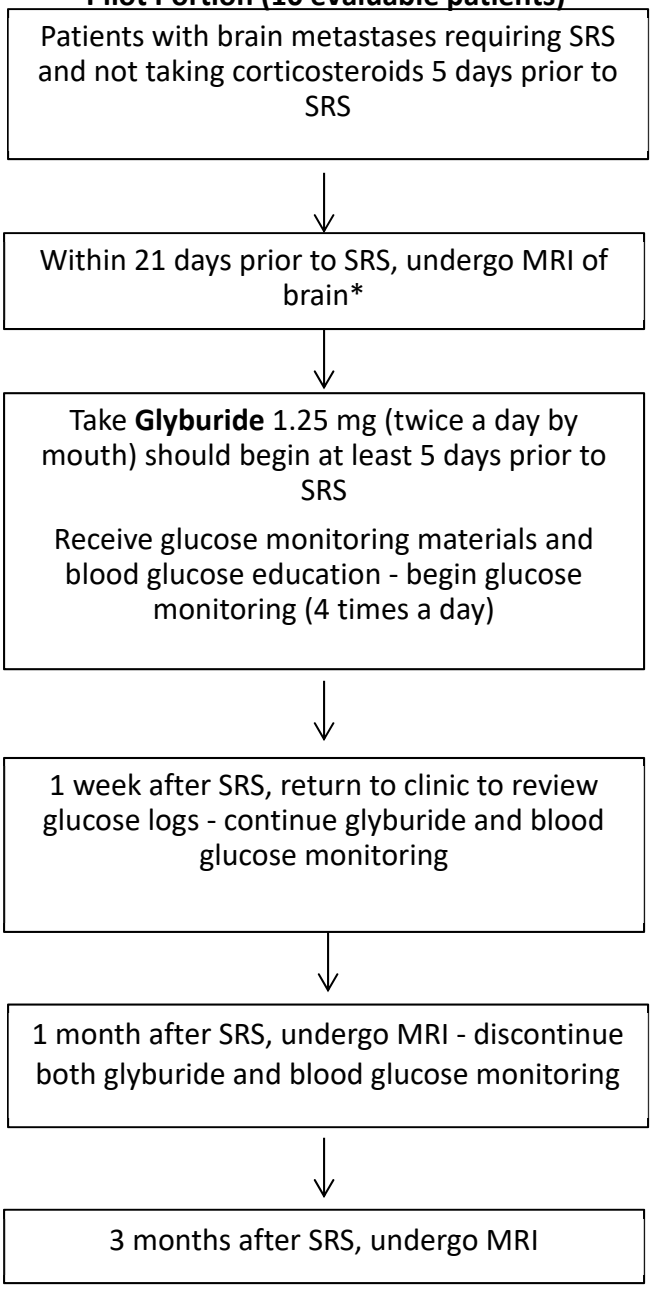
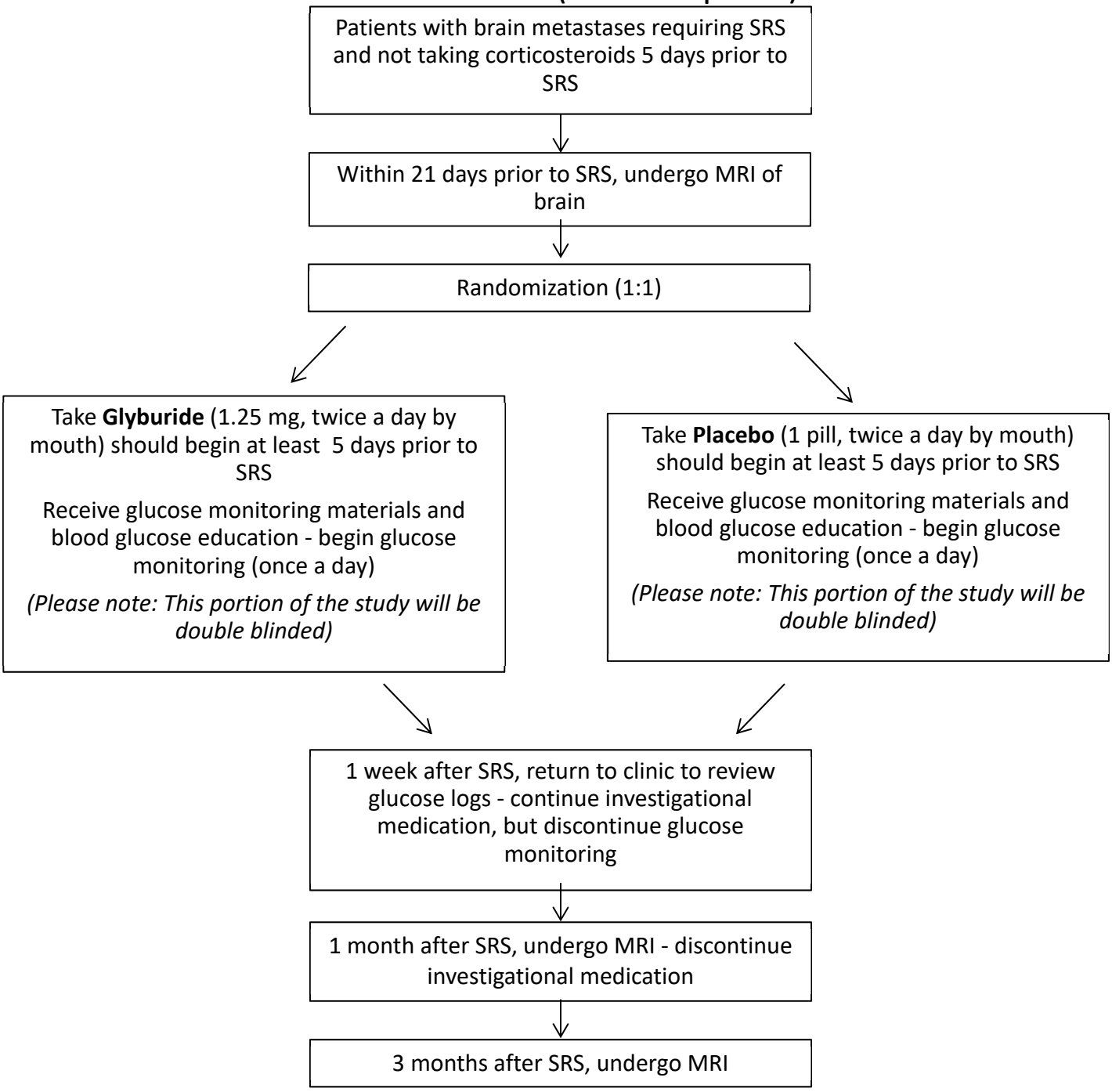
TREATMENT SCHEMA
Pilot Portion (10 evaluable patients)



* Patients undergoing linac-based radiosurgery may have the MRI performed within 21 days prior to SRS treatment (this is for the cases where it is not standard of care to complete a MRI on the day of SRS, as it is with gamma knife).

TREATMENT SCHEMA – Continued…

Randomized Portion (40 evaluable patients)



* Patients undergoing linac-based radiosurgery may have the MRI performed within 21 days prior to SRS treatment (this is for the cases where it is not standard of care to complete a MRI on the day of SRS, as it is with gamma knife).

1.0 INTRODUCTION

1.1 Background

Cerebral metastases affect ~10% of patients diagnosed with cancer. As techniques for local and systemic control of primary tumors improve, the incidence of brain metastases continues to rise. Vasogenic edema associated with brain metastases may result in significant neurologic defects resulting from mass effect. The standard treatment for symptomatic intracerebral edema is glucocorticoids. Administration of 4-8 mg of dexamethasone results in neurologic improvement in up to 75% of patients with brain metastases and significant edema. Dose-dependent toxic effects, such as myopathies, immunosuppression, hypothalamic/pituitary axis suppression etc., limit its long-term use. Other agents to reduce edema, including vascular endothelial growth factor (VEGF) inhibitors such as bevacizumab, show efficacy, but high cost and side effects limit use in most patients with malignancy-induced cerebral edema. The importance of finding an inexpensive, widely available, and well-tolerated agent, either to reduce edema associated with malignancy or to prevent development of edema in selected patients cannot be overstated (1).

Commonly prescribed glucose-lowering agents, especially sulfonylureas, have been of special research interest in preclinical and patient models with central nervous system (CNS)-related cytotoxic and malignant edema. Although in use as an oral hypoglycemic agent since the 1960s, glyburide (glibenclamide) has recently been rediscovered as a potential anti-edema agent. The utilization of glyburide to prevent neurologic deficits secondary to edema has been extensively described in preclinical models of ischemic stroke, subarachnoid hemorrhage, traumatic brain injury, and spinal cord injury. Retrospective studies examining diabetic patients with acute ischemic stroke have associated improved neurologic outcomes, decreased hemorrhagic transformation, and less mortality with glyburide administration. Recently published preclinical studies in mouse models with cerebral metastases have elucidated a potential benefit in prevention of edema using glyburide (2).

1.2 Biologic Background

The mechanism underlying the anti-edema effect of glyburide relates to its inhibition of sulfonylurea receptor 1 (Sur1) nonselective cation channels. The Sur receptors form associations with pore-forming subunits to create transmembrane ion channels. In pancreatic beta cells, Sur1 binds with kir6.2*/KCNJ11* to form adenosine triphosphate (ATP)-sensitive potassium channels. Glyburide's inhibition of Sur1 results in membrane depolarization by an efflux of K+ via the kir6.2 channel. This, in turn, causes an increase in intracellular calcium, which stimulates beta cell insulin release. The Sur1-K_{ATP} channels formed by association with kir6.2 are also present in neurons, where they serve to hyperpolarize and likely neuroprotect the cell by preventing a pathologic rise in intracellular calcium.

In addition, Sur1 associates with the pore-forming *TRPM4* channel, which is a calcium-sensitive nonselective cation channel. When ATP is depleted in the CNS, an inward Na+ flux via the Sur1-*TRPM4* channel results in cell membrane depolarization, which can lead to

necrotic cell death. Unregulated sodium influx causes oncotic cell swelling, which results in cytotoxic edema and ultimately necrotic cell death.

The normal function of the Sur1-*TRPM4* channel is to regulate calcium efflux. It is believed that the primary purpose of the Sur1-*TRPM4* receptor is to prevent a pathologic rise in intracellular calcium levels that occurs during CNS injury. When injury occurs, the channels open to allow for Ca+ efflux but require ATP to close the channels again. In the absence of ATP, as in stroke, hypoxic brain tumors, or traumatic brain injury (TBI), the channel becomes permanently opened (3).

Sulfonylureas, such as glyburide, bind with high affinity to and inhibit Sur1. Sulfonylureas bind to a cytoplasmic loop on Sur1 and prevent closed-state channels from opening but have no effect on channels that are already opened. Of note, the potency of glyburide in binding and inhibiting the Sur1 receptor is increased 8-fold when pH is decreased from 7.4 to 6.8 (Figure 1).

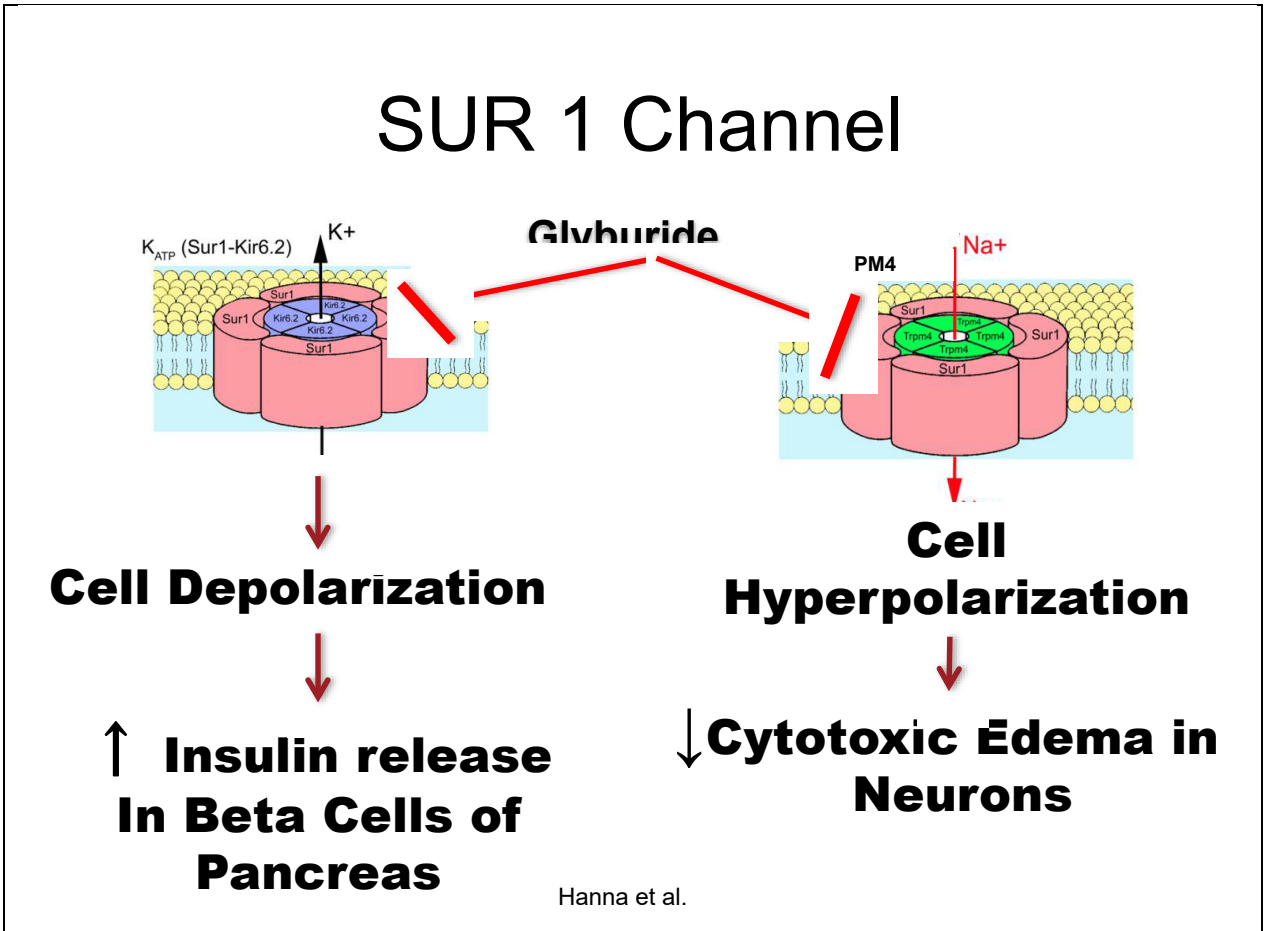


Figure 1

Sulfonylureas are not typically present in therapeutic concentrations in the CNS under nonischemic conditions; however, when acidotic conditions occur after hypoxia and

ischemia, the low pH enhances glyburide's lipid solubility and ability to pass through the blood-brain barrier (BBB). The presence of hypoxia in the brain allows the preferential uptake of glyburide in the CNS at lower doses with less effect on pancreatic insulin secretion (4).

1.3 Sur1 in CNS Injury

Under normal conditions, Sur1-K_{ATP} channels are present in some neurons but are absent in endothelium, oligodendrocytes, most neurons, and astrocytes. Sur1-*TRPM4* channels are not present in normal CNS cells. After CNS injury, Sur1-*TRPM4* channels are spontaneously upregulated in vascular endothelial cells, neurons, and astrocytes as early as several hours after ischemic insult. The mechanism by which this upregulation occurs is complex and ultimately results in transcription of ATP-binding cassette transporter subfamily C member 8 (ABCC8) mRNA. Hypoxia-inducible factor α (HIFα) is a short-lived transcription factor that is activated in the setting of hypoxia. During hypoxia, HIF binds to the Sp1 promoter gene, which then upregulates ABCC8 transcription. ABCC8 then encodes for Sur1 production, which directly leads to an upregulation of Sur1-*TRPM4* channels.

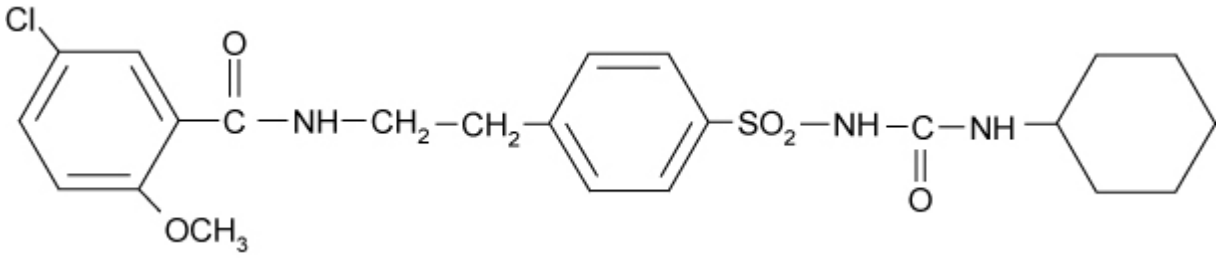
In the setting of CNS inflammation, the nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) binds to a promoter site on ABCC8 and is further stimulated by tumor necrosis factor α (TNFα) exposure. Thus it appears that TNFα and NF-κB are also directly correlated with ABCC8 activation and Sur1 upregulation.

In a study by Simard et al. (5), when mice underwent permanent middle cerebral artery (MCA) occlusion ABCC8 mRNA increased by 2.5-fold at 3 hours, with a 2.5-fold increase in Sur1 channels at 8 hours after ischemic insult. Another model occluded the MCA for 105 min and reperfused the tissue for 60 min. Sur1 was observed only in vascular endothelium 3 hours after insult, at which time point Sur1 also became detectable in neurons. After 24 hours, astrocytes and oligodendrocytes also had upregulated Sur1 expression. No evidence of Sur1 was demonstrated in the necrotic core.

In humans with ischemic stroke, brain autopsy specimens show increased levels of Sur1, predominately in the vascular endothelium and neurons 1 week after insult. Endothelial levels decline after 7 days, and Sur1 becomes increasingly upregulated in microglia and macrophages over the first 31 days (6).

1.4 Investigational Agent – Glyburide (non-micronized)

Glyburide tablets contain glyburide, which is an oral blood-glucose-lowering drug of the sulfonylurea class (7). Glyburide is a white, crystalline compound, formulated as glyburide tablets of 1.25, 2.5, and 5 mg strengths for oral administration. Inactive ingredients include colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, pregelatinized starch, and sodium starch glycolate. In addition, the 2.5 mg tablet contains D&C yellow No. 10 Aluminum Lake and the 5 mg tablet contains FD&C Blue No. 1 Aluminum Lake and D&C Yellow No. 10 Aluminum Lake. The chemical name for glyburide is 1-[[ρ-[2-(5-chloro-o-anisamido)-ethyl]phenyl]-sulfonyl]-3-cyclohexylurea and the molecular weight is 493.99. The structural formula is represented below:



1.4.1 Pharmacokinetics

Single dose studies with glyburide tablets in normal subjects demonstrate significant absorption of glyburide within one hour, peak drug levels at about four hours, and low but detectable levels at twenty-four hours. Mean serum levels of glyburide, as reflected by areas under the serum concentration-time curve, increase in proportion to corresponding increases in dose. Multiple dose studies with glyburide in diabetic patients demonstrate drug level concentration-time curves similar to single dose studies, indicating no buildup of drug in tissue depots. The decrease of glyburide in the serum of normal healthy individuals is biphasic; the terminal half-life is about 10 hours. In single dose studies in fasting normal subjects, the degree and duration of blood glucose lowering is proportional to the dose administered and to the area under the drug level concentration-time curve. The blood glucose lowering effect persists for 24 hours following single morning dose in nonfasting diabetic patients. Under conditions of repeated administration in diabetic patients, however, there is no reliable correlation between blood drug levels and fasting blood glucose levels. A one year study of diabetic patients treated with glyburide showed no reliable correlation between administered dose and serum drug level.

The major metabolite of glyburide is the 4-trans-hydroxy derivative. A second metabolite, the 3-cis-hydroxy derivative, also occurs. These metabolites probably contribute no significant hypoglycemic action in humans since they are only weakly active (1/400th and 1/40th as active, respectively, as glyburide) in rabbits.

Glyburide is excreted as metabolites in the bile and urine, approximately 50% by each route. This dual excretory pathway is qualitatively different from that of other sulfonylureas, which are excreted primarily in the urine.

Sulfonylurea drugs are extensively bound to serum proteins. Displacement from protein binding sites by other drugs may lead to enhanced hypoglycemic action. In vitro, the protein binding exhibited by glyburide is predominantly non-ionic, whereas that of other sulfonylureas (chlorpropamide, tolbutamide, tolazamide) is predominantly ionic. Acidic drugs such as phenylbutazone, warfarin, and salicylates displace the ionic-binding sulfonylureas from serum proteins to a far greater extent than the non-ionic binding glyburide. It has not been shown that this difference in protein binding will result in fewer drug-drug interactions with glyburide tablets in clinical use.

1.4.2 Drug Properties

Synonyms include: Glibenclamide, Glybenzcyclamide, and Glyburide.

1.4.3 Physicochemical Properties

1.4.3.1 *Molecular Weight* = 493.99

1.4.3.2 *pKa* = 5.3

1.4.3.3 *Solubility* = The aqueous solubility of DiaBeta(R) increases with pH as a result of salt formation.

1.4.4 Storage and Stability

1.4.4.1 *Preparation*

Oral route: Tablets should be administered with breakfast or the first main meal of the day and in the evening with dinner.

Tablets should be stored at controlled room temperature, between 20 and 25 degrees C (68 and 77 degrees F).

1.4.5 Onset

1.4.5.1 *Initial Response* = Non-insulin dependent diabetes mellitus (NIDDM), oral: 30 minutes.

1.4.5.2 *Peak Response* = NIDDM, oral: 2 to 3 hours.

1.4.6 Duration

1.4.6.1 *Multiple Dose* = NIDDM, oral: 24 hours.

1.4.7 Therapeutic Drug Concentration

Plasma/serum range considered therapeutic ('normal') was stated to be 0.05 to 0.2 mcg/mL.

1.4.8 Time to Peak Concentration

1.4.8.1 *Oral, non-micronized* = 4 hours.

After a single dose of glyburide 7 mg, the maximum concentration for glyburide was 302 (tmax 1.5 hours) and 463 ng/mL (tmax 1.4 hours), respectively, in diabetic patients with impaired (range 7 to 42 mL/min/1.73 m^2) and normal renal function.

After a single dose of glyburide 7 mg, the maximum concentration for the glyburide metabolite (M1) was significantly higher at 36 ng/mL in diabetic patients with impaired renal function (range 7 to 42 mL/min/1.73 m^2) compared to 26 ng/mL in diabetic patients with normal renal function.

1.4.9 Area Under the Curve (AUC)

568 ng/hour/mL.

The AUC for non-micronized glyburide 5 mg is 746 ng/hour/mL.

After a single dose of glyburide 7 mg, the area under the curve (AUC) for glyburide was 1153 and 2086 ng x L/hr, respectively, in diabetic patients with impaired (range 7 to 42 mL/min/1.73 m^2) and normal renal function.

1.4.10 Absorption

1.4.10.1 *Bioavailability*: Oral, non-micronized = well absorbed.

1.4.10.2 *Effects of Food*: Clinically insignificant. Food does not affect the rate or extent of absorption.

1.4.11 Distribution

1.4.11.1 *Distribution Sites*: Protein Binding = 99%.

1.4.11.2 *Distribution Kinetics*: Distribution Half-Life = 20 to 30 minutes.

1.4.12 Metabolism

1.4.12.1 *Metabolism Sites and Kinetics*: Liver, extensive.

1.4.12.2 *Metabolites*: Include 4-trans-hydroxyglyburide and 3-cis-hydroxyglyburide.

1.4.12.2.1 4-trans-hydroxyglyburide, active. This metabolite is weakly active. This metabolite was about 75% as active as the parent compound in a small study.

1.4.12.2.2 3-cis-hydroxyglyburide, weakly active. This metabolite was about 50% as active as the parent compound in a small study.

1.4.13 Excretion

1.4.13.1 *Kidney*: Renal Excretion (%) = 50%. At 24 hours, only 7.2% of the glyburide metabolites (M1 and M2) was excreted in the urine of diabetic patients with impaired renal function (range 7 to 42 mL/min/1.73 m^2) compared to 26.4% in diabetic patients with normal renal function.

1.4.13.2 *Other*: Bile = 50%.

1.4.14 Elimination Half-life

Parent Compound's elimination half-life = 5 to 10 hours.

1.5 Preclinical Data

Rat stroke models have been used extensively to study glyburide and Sur1 inhibition. Intraperitoneal administration of 10 µg/kg of glyburide followed by a constant infusion of 200 ng/h up to 5.75 hours after ischemic insult resulted in up to 50% reduction in edema volumes. Measurable reductions in neurologic deficits, assessed by grip strength, hemispheric swelling, and infarct volumes, in rats have also been observed. Glyburide administration secondary to infarction and cerebral edema resulted in reduction in mortality rates from 65% to 24% at 7 days after administration (no loading dose with 75 ng/h infusion). In a study comparing the efficacy of glyburide with that of decompressive craniectomy after 6 hours of MCA occlusion, glyburide-treated rats showed reduced 24 hour brain edema and measurably improved neurologic outcomes persisting through the 14 day observation period (8).

In animal models in which subarachnoid hemorrhage was induced, glyburide reduced edema formation by inhibition of endothelial cytoskeleton rearrangement, thereby decreasing BBB permeability. Intracerebral hemorrhage results in upregulation of inflammatory markers such as TNFα and NF-κB, which, as noted, are directly related to upregulation of Sur1-*TRPM4* channels. As seen in other injury models, these levels were decreased with glyburide administration.

In TBI models, mice with focal cerebral contusions were found to have upregulated Sur1 levels, likely related to hemorrhagic progression. Levels became elevated as early as a few hours after insult and continued to increase throughout the first 24 hours. As with subarachnoid hemorrhage, this resulted in increased cytokine release and subsequent edema formation through Sur1-related pathways. Glyburide administration up to 24 hours after trauma decreased the hemorrhagic progression of the lesion, resulting in smaller lesion size and reduced edema.

Traumatic spinal cord injuries also exhibit endothelial damage resulting in hemorrhagic progression and hemorrhagic necrosis. Sur1 is found to be present at 6 hours following spinal cord injury and increases in expression mostly in the periphery of the necrotic lesion within the first 24 hours, showing specific upregulation along the capillaries and neurons. Administration of glyburide reduces progression to hemorrhagic necrosis by decreasing fragmentation of capillaries and damage to white matter spinal tracts. Edema volumes continue to be substantially reduced and functional outcomes improved at 1-6 weeks following injury with glyburide administration when compared with controls (1).

1.6 Glyburide in Cancer

The presence of Sur1 upregulation in intracerebral malignancies and the effectiveness of glyburide at inhibiting edema were reported in a landmark study by Thompson et al (2). In this study, mice underwent intracerebral injection of LX1 human small-cell lung carcinoma (SCLC), UW28 malignant glioma, and A2058 human melanoma cells into the right basal ganglia. A baseline dynamic contrast-enhanced magnetic resonance (DCE-MR) image was obtained 7-10 days after intracerebral implantation. DCE-MR imaging uses a transfer coefficient (K_{trans}) that measures permeability of blood vessels and extravascular extracellular space volume fraction (V_e). When the BBB is intact, K_{trans} = 0/min and V_e is unmeasurable. Only when contrast leaks from the vessel is V_e measurable. One day after baseline DCE-MR imaging, animals received either vehicle, intravenous (IV) dexamethasone (0.35 mg in a single dose), or oral glyburide (2 administrations of 4.8 µg solution 8 hours apart). A post-treatment DCE-MR image was obtained 48 hours after baseline DCE-MR imaging. Immediately afterward, a continuous IV infusion of vehicle, dexamethasone (3 µg/h), or glyburide (400 ng/h) was administered. Blood glucose was routinely monitored. Animals that suffered > 20% weight loss or marked neurologic impairment were sacrificed.

The results in this study showed first that Sur1 was upregulated in the implanted basal ganglia compared to the contralateral uninvolved basal ganglia. As was seen in prior ischemic stroke models, little Sur1 was expressed in normal brain parenchyma, but Sur1 was demonstrably

increased in SCLCs and in the melanoma models both on immunohistochemistry and Western blot analyses. Upregulation was noted in glial and endothelial cells. Sur1 expression did not differ significantly among the three treatment groups.

K_{trans}, and postgadolinium T1 and T2 tumor areas did not differ among the treatment groups at the time of the baseline scan. Glyburide was found to significantly decrease K_{trans} at the time of post-treatment DCE-MR imaging (signifying decreased blood-tumor barrier permeability) compared with vehicle in the SCLC and melanoma groups. Interestingly, dexamethasone significantly decreased K_{trans} when compared with vehicle in the SCLC model but not in the melanoma model.

1.7 Clinical Data to Date

As noted, retrospective studies in diabetic patients taking glyburide who suffer ischemic stroke have shown associations with improved National Institutes of Health (NIH) Stroke Scale scores, functional improvement, and decreased hemorrhagic transformation compared with patients not taking glyburide. In one study, patients taking a sulfonylurea at the time of major ischemic stroke had a decreased in-hospital mortality rate (11% with control vs 0% in patients taking sulfonylurea).

The Glyburide Advantage in Malignant Edema and Stroke (GAMES) Pilot is a two-center adaptive phase II study that as of October 2, 2013, has completed enrollment of the pilot portion and is currently enrolling patients in the phase II randomized portion. In the pilot phase, 10 patients who experienced severe anterior circulation ischemic stroke with infarct volumes ≥ 82 mL received RP-1127 (IV glyburide infusion over 72 hours). Infarct volumes ≥ 82 mL in stroke are associated with a > 85% chance of developing malignant edema (9). Primary outcomes are feasibility and safety; secondary objectives are measurement of clinical endpoints, such as Glasgow Coma Scale, NIH Stroke Scale, and Full Outline of Unresponsiveness scores. Eight of the initial 10 patients in the GAMES pilot required no intubation, decompressive craniectomy, or osmotherapy (such as mannitol). One patient required decompressive craniectomy and ultimately died. No significant hematoma formations were observed in the group, compared with a 30% rate of clinically significant hematoma formation in a previously published series not utilizing glyburide. The modified Rankin Score (mRS) measures performance status in patients suffering stroke on a scale from 0 (no symptoms) to 6 (dead), with a score of 4 denoting moderately severe disability. In the GAMES trial, 90% of patients had 30 day mRSs of ≤ 4, whereas only 29% of stroke patients in a control cohort had similar scores at 90 days.

The randomized portion of the GAMES trial is currently accruing (with a maximum accrual of 240 patients) and randomizes patients to RP-1127 versus placebo (10). Primary endpoints include number of patients with mRS scores ≤ 4 at 90 days who do not need decompressive craniectomy, rates of malignant edema development, and safety. Secondary endpoints will evaluate neurologic deterioration, parenchymal hematoma development, hemispheric swelling evaluated by MR imaging, activities of daily living, and mortality rates. Projected accrual completion is February 2015.

1.8 Study Rationale

The most common side effect of glyburide is hypoglycemia. Sulfonylureas carry a rare but serious risk of increased cardiovascular mortality. Although the risk of cardiovascular mortality in patients receiving tolbutamide, a first-generation sulfonlyurea, was 2.5 times that of patients treated with diet alone, subsequent studies have indicated that glyburide is not associated with an increased risk of cardiovascular events. A rare sulfonylurea-associated risk is hemolytic anemia in patients with G6PD deficiency and, in even more rare instances, in those without.

In contrast, dexamethasone causes disturbances in glucose metabolism in approximately 50% of patients, in addition to immunosuppression, femoral avascular necrosis, thrush, psychiatric disorders, and Cushing syndrome, among others.

In addition to a favorable side effect profile, the cost/benefit considerations of glyburide over alternatives merit consideration. The cost of a 30 day supply of glyburide is approximately $30, compared with $22 for dexamethasone. The cost of bevacizumab is approximately $9,000/month.

Stereotactic radiosurgery (SRS) for brain metastases results in an approximately 5% incidence of radiation induced neurologic morbidity. Current interventional options include corticosteroids, pentoxifylline and vitamin E, surgery, hyperbaric oxygen, anticoagulation, and interstitial laser thermal therapy. More recently, bevacizumab has been shown to reduce T2/fluid-attenuated inversion recovery volumes on MR in patients with presumed SRS-induced radiation effects. A 90% improvement in neurologic symptomatology was noted; however, 61% of those patients experienced a return of neurologic symptomatology after discontinuation of anti-VEGF therapy. Because of the side-effect profile and high cost of anti-VEGF therapies, glyburide becomes an intriguing alternative as either prophylaxis against potential development of edema induced from radiotherapy or as a treatment alternative for existing edema that is at risk of becoming more significant with radiotherapy (1).

Developing a mechanism to predict which patients are at highest risk of developing edema after SRS is important when designing a potential randomized trial in order to select patients who may benefit most from prophylactic oral glyburide administration. A retrospective analysis at the University of Maryland Medical Center, Department of Radiation Oncology examined 55 patients treated with SRS using the Gamma Knife for brain metastases and analyzed potential predictors for volumetric increase in edema from MR imaging obtained no more than 30 days before SRS, compared with post-treatment MR imaging obtained no later than 100 days after SRS. Multivariate analysis of preliminary data suggests that melanoma/renal primary histology, Recursive Partitioning Analysis class III, large pre-treatment edema-to-tumor ratio, and prior whole brain therapy all increase the risk of volumetric edema increase after SRS. Patients with melanoma/renal primaries had a lower pre-treatment edema volume than other primaries but had the largest increase in edema

after SRS when compared to those with other histologies (Figure 2). Patients that possessed 2 or more of these risk factors had a 35% chance of volumetric edema increase as measured on axial T2 imaging as compared to an 8% risk of edema increase in patients with less than 2 risk factors. Edema increase was measured from time of MRI obtained no earlier 30 days prior to SRS compared to MRI obtained no later than 100 days after SRS. Absolute edema was calculated by subtracting the contoured tumor volume from the contoured edema volume. Absolute edema that was < 1.00 cc was not considered edema. Edema increase was defined as an absolute increase in 5% from the time of pre SRS MRI to the time of post SRS MRI.

Variable	Edema increase	No edema increase	% with increased edema	*P* value*
Primary histology				
Melanoma or RCC	9	15	38%	
Others	14	76	16%	
				0.0239
RPA class				
I or II	11	72	13%	
III	10	21	32%	
				0.0292
Metastasis location				
Infratentorial	1	23	4%	
Supratentorial	20	70	22%	
				0.0711
Prior WBRT				
Yes	17	53	24%	
No	4	40	9%	
				0.049

Figure 2: Data from Hanna et al. demonstrates odds of developing increased cerebral edema associated with certain risk factors (15).
RCC: Renal Cell Carcinoma / WBRT: whole brain radiation therapy

In considering the potential benefit of glyburide in these patients, recall that Thompson's study showed a statistically significant decrease in ADC levels in mice that received glyburide compared to vehicle. The reduction in ADC with dexamethasone compared to vehicle was not significant. This raises an interesting question as to whether the mechanism of edema formation induced by radiotherapy is different in melanoma/renal histologies from that in other primary types and may be more responsive to glyburide administration (15). DCE-MR imaging to determine pre- and post-treatment intracerebral vascular permeability levels (as

assessed in Thompson's study) may contribute to a more informed evaluation of the potential benefits of glyburide in patients. Patients on the GAMES Pilot study had comparisons of cytotoxic edema formation to historical controls. FLAIR intensity (which is a marker for subsequent vasogenic edema formation) was standardized by normalizing the value to the contralateral hemisphere to make a so called "FLAIR ratio". This ratio was significantly less in patients receiving infusional glyburide compared to historical control, signifying less vasogenic edema. Utilization of edema volumes is a potential tool to quantify glyburide's effect to reduce edema in future studies (11).

1.9 Dose Rationale and Risk/Benefits

No human trials have yet been undertaken to evaluate the use of glyburide in reducing edema in patients with intracerebral malignancies. In Thompson's study, the human dose equivalent of glyburide would be 2.5 mg/d for a 70 kg patient (2). No adverse mouse-related hypoglycemic events were noted with comparative levels of administration. Typical oral doses of glyburide in diabetic patients range from 2.5 to 20 mg/d. The starting dose is usually a single 2.5 mg tab/day, but this can be divided into twice-per-day administrations of 1.25 mg if patients are at risk of developing hypoglycemia. Human trials in ischemic stroke currently use the IV infusion form of glyburide (RP-1127), which has less potential for hypoglycemia and is not dependent on stomach pH. In a current phase I trial evaluating tolerability in healthy volunteers, RP-1127 is given as bolus followed by 72 hour continuous infusion. No serious adverse events have been reported. Two patients with persistent hypoglycemia (at 6 mg/d and 10 mg/d) were discontinued from the study, and one patient (at 6 mg/d) had a transient asymptomatic increase in aminotransferase/alanine aminotransferase levels. In this dose-finding study, 3 mg/d seemed the safest dose to yield therapeutic serum levels while minimizing hypoglycemic risk (12).

Utilization of infusional glyburide makes sense in patient populations that are critically ill and in an intensive care settings, but trials utilizing oral glyburide are more feasible in outpatient settings. However, no data currently exists proving that oral glyburide is safe in the non-diabetic population. The Glyburide Healthy Volunteer Study is currently enrolling non-diabetic participants who take 1.5 mg/d of glyburide with breakfast. This study is designed to assess potential use of prophylactic glyburide to mitigate TBI in military personnel. As part of the trial, enrollees undergo strenuous physical activity and are monitored for hypoglycemia, dizziness, and/or confusion. Serial glucose monitoring and neuropsychological testing, as well as electrocardiographic and laboratory values, are collected and monitored during the 7 day inpatient study. These results have not yet been reported (13). As such, we aim to undertake a safety study in patients with brain metastases receiving oral glyburide followed by a randomized study to assess the effect of glyburide on peritumoral edema in patients with a high risk of edema increase after stereotactic radiosurgery.

2.0 OBJECTIVES AND ENDPOINTS

2.1 Primary Objectives

2.1.1 Pilot Portion: To determine the feasibility and safety of administering oral glyburide to non-diabetic patients receiving stereotactic radiosurgery (SRS) for newly diagnosed brain metastases.

2.1.2 Randomized Portion: To determine the number of patients with newly diagnosed brain metastases who have an increase in edema as measured on volumetric FLAIR imaging and the number of patients that require dexamethasone administration (or any corticosteroid administration with the purpose of treating cerebral edema) from the day of SRS* to one month follow-up MRI in the group receiving glyburide versus placebo.

2.2 Secondary Objectives (Randomized Portion)

2.2.1 To assess the FLAIR Volume degree of change between the treatment groups.

2.2.2 To assess the rate of symptomatic progression requiring dexamethasone (or any corticosteroid administration with the purpose of treating cerebral edema) between the treatment groups.

2.2.3 To assess differences in local control between the treatment groups.

2.2.4 To assess differences in neurologic toxicities between the treatment groups.

2.2.5 To assess differences in cardiac and hepatobiliary toxicities between the treatment groups.

2.3 Primary Endpoints

2.3.1 Pilot Portion: Occurrence of Dose Limiting Toxicities (DLTs) between the time of glyburide initiation and the time of the one month follow-up MRI.

2.3.2 Randomized Portion: Occurrence of edema increase and initiation of dexamethasone (or any corticosteroid administration with the purpose of treating cerebral edema) between the time of SRS* and the time of the one month follow-up MRI.

2.4 Secondary Endpoints

2.4.1 Pilot Portion

2.4.1.1 Time until dexamethasone initiation (or any corticosteroid administration with the purpose of treating cerebral edema) as measured between the time of SRS* and the time of the one and three month post SRS MRI scans.

2.4.1.2 Incidence of CTCAE version 4.0 reportable toxicities of grades 2-5.

2.4.1.3 Incidence of CTCAE version 4.0 reportable toxicities of grades 1-2 Cardiac Disorders or Hepatobiliary Disorders.

2.4.1.4 Cerebral edema increase as measured on FLAIR volumetric imaging, defined from MRI taken at the time of SRS* and the time of the one and three month post SRS MRI scans.

2.4.1.5 Absolute volume change of index tumor(s) that received radiosurgery as manually contoured by the radiation oncologist defined from T1 post gadolinium sequences at the time of SRS* and the time of the one and three month post SRS MRI scans.

2.4.2 Randomized Portion

2.4.2.1 Dexamethasone initiation (or any corticosteroid administration with the purpose of treating cerebral edema) between the treatment groups (as measured between the time of SRS* and the time of the one and three month post SRS MRI scans).

2.4.2.2 Rate of CTCAE version 4.0 grade 2-5 Nervous system disorder toxicities between the treatment groups.

2.4.2.3 Rate of CTCAE version 4.0 grade 1-5 Cardiac Disorders and Hepatobiliary Disorders between the treatment groups.

2.4.2.4 Comparison of mean rate of cerebral edema increase as measured on FLAIR volumetric imaging between the treatment groups (defined from MRI taken at the time of SRS* and the time of the one and three month post SRS MRI scans).

2.4.2.5 Comparison of median absolute volume change of index tumor(s) that received radiosurgery as manually contoured by the radiation oncologist between the treatment groups (defined from T1 post gadolinium image at the time of SRS* and the time of the one and three month post SRS MRI scans).

* Please note that the MRI may be performed within 21 days prior to SRS treatment only if the patient is being treated with linac-based radiosurgery and it is not standard of care to complete a MRI on the day of SRS (as it is with gamma knife).

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility

3.1.1 Patients with newly diagnosed brain metastases deemed to be eligible for radiosurgery.

3.1.1.1 Prior whole brain RT and radiosurgery (to areas outside of the newly diagnosed brain metastases requiring radiosurgery) is allowed

3.1.2 Subject must have cytologically or histologically confirmed malignancy (this is the original malignancy, not the brain metastases).

3.1.3 A diagnostic contrast-enhanced MRI of the brain must be performed within 60 days prior to registration. The contrast-enhancing intraparenchymal brain tumor must be well visualized.

3.1.4 History and physical with neurological examination, height, and weight within 14 days prior to registration.

3.1.5 No dexamethasone use (or any other corticosteroid use with the purpose of treating cerebral edema) starting 5 days prior to SRS. Patients may be tapered to meet this criterion if deemed safe by the treating physician.

3.1.6 Women of child-bearing potential (e.g. not post-menopausal or permanently sterilized women) must have a negative pregnancy test obtained within 14 days prior to registration. This is to prevent potential harm to the fetus by glyburide and radiotherapy.

3.1.7 Age ≥ 18 years of age.

3.1.8 Complete Blood Count (CBC) with differential and a Comprehensive Metabolic Panel (CMP) including Liver Function Tests (LFTs) obtained within 14 days prior to registration and meeting the following requirements:

- Creatinine Clearance ≥ 50 mL/min (by Cockcroft-Gault Equation).

- Total Bilirubin < 1.5 x the upper limit of normal (ULN).
- ALT and AST ≤ 2.5 x ULN.
- Glucose ≥ 80 mg/dL.
- Hemoglobin ≥ 7 mg/dL.
- Absolute Neutrophil Count > 100 cells/mm3.

3.1.9 <u>For the Randomized Portion only:</u>

3.1.9.1 Subject must have at least 2 of the following risk factors:

- Pretreatment Edema/Tumor ratio (≥ 35:1) as contoured on a baseline MRI obtained at most 60 days prior to registration. Patients are allowed to have Whole Brain Radiotherapy (WBRT) or corticosteroid use between the time of pretreatment MRI and SRS (as long as the corticosteroids can be safely tapered at least 5 days prior to the treatment planning MRI and WBRT is at least 4 days prior to registration).
- Greater than 40 pack year history of smoking cigarettes.
- Whole Brain Radiotherapy at least 4 days and no more than 1 year prior to registration.
- RPA Class III.

3.1.10 <u>For the Pilot Portion</u>, it is not required that patients have the risk factors mentioned in 3.1.9.

3.2 Conditions for Patient Ineligibility

3.2.1 Known sulfonylurea treatment within 7 days prior to registration. Sulfonylureas include glyburide/glibenclamide (Diabeta, Glynase); glyburide plus metformin (Glucovance); glimepiride (Amaryl); repaglinide (Prandin); nateglinide (Starlix); glipizide (Glucotrol, GlibeneseR, MinodiabR); gliclazide (DiamicronR); tolbutamide (Orinase, Tolinase); and glibornuride (Glutril).

3.2.2 Diffuse Leptomeningeal metastases.

3.2.3 Known allergy to sulfa or specific allergy to sulfonylurea drugs.

3.2.4 Use of VEGF inhibitors within 10 days prior to registration.

3.2.5 Allergy to gadolinium.

3.2.6 Type 1 diabetes mellitus or Type 2 diabetes mellitus actively receiving treatment.

3.2.7 Cognitive impairment that precludes a patient from acting as his or her own agent to provide informed consent.

3.2.8 Concurrent use of Bosentan.

3.2.9 Any major medical illnesses or psychiatric impairments that in the treating physician's opinion will prevent administration or completion of protocol therapy (which may include patients who are elderly, debilitated, or malnourished persons and/or those with renal, hepatic or adrenal insufficiency).

3.2.10 Pregnant or breast feeding women due potential damage to the fetus.

3.2.11 Inability to undergo MRI or SRS (e.g. due to safety reasons such as presence of a pacemaker).

3.2.12 Deemed by the treating physician to be unable to eat regular meals.

3.2.13 Patients currently on beta blockers.
3.2.14 Patient with a known diagnosis of ongoing alcoholism/alcohol abuse.

4.0 PATIENT TREATMENT EVALUATIONS

* Due to COVID-19, these study procedures may be conducted remotely, if necessary.

4.1 Pilot Portion

4.1.1 Within 60 days prior to registration

4.1.1.1 Contrast-enhanced MRI of the brain (may be performed at an outside institution).

4.1.2 Within 14 days prior to registration

4.1.2.1 History and Physical with height, weight, neurological exam and corticosteroid use documentation. If using dexamethasone (or any other corticosteroid with the purpose of treating cerebral edema), must implement a plan to have this safely discontinued by 5 days prior to SRS.

4.1.2.2 Complete Blood Count (CBC) with differential and a Comprehensive Metabolic Panel (CMP) including Liver Function Tests (LFTs).

4.1.2.3 Pregnancy test for women of child-bearing potential.

4.1.3 Within 21 days prior to SRS

4.1.3.1 All patients will have a brain MRI with and without contrast suitable for SRS planning. T1-weighted, T2 and/or FLAIR MRI of the brain (maximum slice thickness 5mm). FLAIR imaging is preferred.

4.1.3.1.1 T1 post gadolinium sequence will be imported into the Eclipse treatment planning system and the radiation oncologist will contour the enhancing tumor that received the prescribed dose of SRS.

4.1.3.1.2 FLAIR sequence will be imported into the Eclipse treatment planning system. FLAIR volume will be automatically calculated using "Region Growing" on Eclipse (Appendix I). The automated contours will be verified and modified as needed by the radiation oncologist.

4.1.3.1.3 The MRI should be performed within 21 days prior to SRS treatment. A repeat treatment planning MRI is allowed. This MRI must meet the descriptions stated above in 4.1.3.1

4.1.4 5-9 days prior to SRS

4.1.4.1 Documentation of corticosteroid use/no dexamethasone (or any other corticosteroid with the purpose of treating cerebral edema) use.

4.1.4.2 Give patient a sufficient supply of non-micronized Glyburide tablets (1.25 mg) to be taken orally twice a day (in the morning with breakfast and in the evening with dinner). Missed doses will not be made up. Patient should be instructed to begin glyburide at least 5 days prior to SRS and continue glyburide until the evening dose of the one month post SRS MRI scan.

4.1.4.3 Provide patient with study supplies that include a medication/blood glucose log (for recording time of taking glyburide as well as time and value of blood glucose draws), a blood glucose monitor, and handouts for education purposes. The patient will be educated on how to measure and record blood glucose values (see Appendices II-VI).

4.1.4.4 Patient should begin fingerstick glucose draws 4 times a day beginning the day of glyburide initiation (in the morning before breakfast [fasting], before lunch, before dinner, and before bed). An additional fingerstick glucose draw will be taken by the nurse/research team member at this visit.

4.1.5 Day of SRS

4.1.5.1 Documentation of corticosteroid use/no dexamethasone (or any other corticosteroid with the purpose of treating cerebral edema) use.

4.1.5.2 Continued fingerstick glucose draws by patient 4 times a day (in the morning before breakfast (fasting), before lunch, before dinner, and before bed) for at least 1 week after SRS.

4.1.6 1 week after SRS (± 3 days)

4.1.6.1 Review the patient's blood glucose and medication administration logs.

4.1.6.2 CBC with differential and CMP including LFTs.

4.1.6.3 Fingerstick Glucose draw by nurse/research team member.

4.1.6.4 Adverse event evaluation. If no "*concerning toxicity*" or "*serious toxicity*" (see section 5.3.1), then patient will be instructed to only obtain fingerstick glucose draws once a day (in the morning before breakfast [fasting]) until the day of discontinuation of glyburide.

4.1.6.4.1 If the patient does have a "*concerning toxicity*" or "*serious toxicity*" they must discontinue glyburide (see section 5.3.1) and thus can also discontinue with their fingerstick glucose draws.

4.1.6.5 Documentation of corticosteroid usage (record the date of initiation, dose and reason for initiation of any new corticosteroid, especially dexamethasone).

4.1.7 1 month after SRS (- 5 or +10 days)

4.1.7.1 Discontinue glyburide (last dose is taken the evening of obtaining the follow-up MRI) and discontinue blood glucose monitoring. Have patient return all remaining (untaken) glyburide tablets.

4.1.7.2 Follow-up brain MRI with and without contrast. T1-weighted, T2 and/or FLAIR MRI of the brain (maximum slice thickness 5mm). FLAIR imaging is preferred.

4.1.7.2.1 T1 post gadolinium sequence will be imported into the Eclipse treatment planning system and the radiation oncologist will contour the enhancing tumor that received the prescribed dose of SRS.

4.1.7.2.2 FLAIR sequence will be imported into the Eclipse treatment planning system. FLAIR volume will be automatically calculated using "Region

Growing" on Eclipse (Appendix I). The automated contours will be verified and modified as needed by the radiation oncologist.

4.1.7.3 Follow-up history and physical with neurologic examination and corticosteroid use documentation (record the date of initiation, dose and reason for initiation of any new corticosteroid, especially dexamethasone). A last fingerstick glucose draw will be done by the nurse/research team member at this visit.

4.1.7.4 Review and collect the patient's blood glucose and medication administration logs.

4.1.7.5 Adverse event evaluation.

4.1.7.6 CBC with differential and CMP including LFTs.

4.1.8 3 months after SRS (- 10 or +14 days)

4.1.8.1 Follow-up brain MRI with and without contrast. T1-weighted, T2, and/or FLAIR MRI of the brain (maximum slice thickness 5mm). FLAIR imaging is preferred.

4.1.8.1.1 T1 post gadolinium sequence will be imported into the Eclipse treatment planning system and the radiation oncologist will contour the enhancing tumor that received the prescribed dose of SRS.

4.1.8.1.2 FLAIR sequence will be imported into the Eclipse treatment planning. FLAIR volume will be automatically calculated using "Region Growing" on Eclipse (Appendix I). The automated contours will be verified and modified as needed by the radiation oncologist.

4.1.8.2 Follow-up history and physical with neurologic examination and corticosteroid use documentation (record the date of initiation, dose and reason for initiation of any new corticosteroid, especially dexamethasone).

4.1.8.3 Adverse event evaluation.

4.1.8.4 CBC with differential and CMP including LFTs.

4.1.9 Conditions for early patient stopping of glyburide

4.1.9.1 A dose limiting toxicity (DLT) is reached. See section 5.3.1.

4.1.9.2 Patient requires corticosteroid administration after registration but prior to SRS, please note these patients will be deemed inevaluable.

4.2 Randomized Portion

4.2.1 Within 60 days prior to registration

4.2.1.1 Contrast-enhanced MRI of the brain (may be performed at an outside institution).

4.2.2 Within 14 days prior to registration

4.2.2.1 History and Physical with height, weight, neurological exam and corticosteroid use documentation. If using dexamethasone (or any other corticosteroid with the purpose of treating cerebral edema), must implement a plan to have this safely discontinued by 5 days prior to SRS.

4.2.2.2 Complete Blood Count (CBC) with differential and a Comprehensive metabolic panel (CMP) including Liver Function Tests (LFTs).

4.2.2.3 Pregnancy test for women of child-bearing potential.

4.2.3 Within 21 days prior to SRS

4.2.3.1 Follow-up brain MRI with and without contrast. T1-weighted, T2, and/or FLAIR MRI of the brain (maximum slice thickness 5mm). FLAIR imaging is preferred.

4.2.3.1.1 T1 post gadolinium sequence will be imported into the Eclipse treatment planning system and the radiation oncologist (who will be blinded to the patient's investigational medication) will contour the enhancing tumor that received the prescribed dose of SRS.

4.2.3.1.2 FLAIR sequence will be imported into the Eclipse treatment planning system. FLAIR volume will be automatically calculated using "Region Growing" on Eclipse (Appendix I). The automated contours will be verified and modified as needed by the radiation oncologist who will be blinded to the patient's investigational medication.

4.2.4 5-9 days prior to SRS

4.2.4.1 Randomization will occur (can be any time after registration/study entry and up until 5-9 days prior to SRS).

4.2.4.2 Documentation of corticosteroid use/no dexamethasone (or any other corticosteroid with the purpose of treating cerebral edema) use.

4.2.4.3 Give patient a sufficient supply of investigational medication: either non-micronized Glyburide tablets (1.25 mg) or placebo, to be taken orally twice a day (in the morning with breakfast and in the evening with dinner). Missed doses will not be made up. Patient, physicians, and the study team will be blinded to the investigational medication. Patient should be instructed to begin investigational medication at least 5 days prior to SRS and continue investigational medication until the evening dose of the one month post SRS MRI scan.

4.2.4.4 Provide patient with study supplies that include a medication/blood glucose log (for recording time of taking the investigational medication as well as time and value of blood glucose draws), a blood glucose monitor, and handouts for education purposes. The patient will be educated on how to measure and record blood glucose values (see Appendices II-VI).

4.2.4.5 Patient should begin fingerstick glucose draws once a day beginning the day of investigational medication initiation (in the morning before breakfast [fasting]). Please see section 5.4.2 for further details. An additional fingerstick glucose draw will be taken by the nurse/research team member at this visit.

4.2.5 Day of SRS

4.2.5.1 Documentation of corticosteroid use/no dexamethasone (or any other corticosteroid with the purpose of treating cerebral edema) use.

4.2.5.2 Continued fingerstick glucose draws by patient once a day (in the morning before breakfast [fasting]) for at least 1 week after SRS. Please see section 5.4.2 for further details.

4.2.6 1 week after SRS (± 3 days)

4.2.6.1 Review the patient's blood glucose and medication administration logs.

4.2.6.2 CBC with differential and CMP including LFTs.

4.2.6.3 Fingerstick Glucose draw by nurse/research team member.

4.2.6.4 Adverse event evaluation. If no "*concerning toxicity*" or "*serious toxicity*" (see section 5.3.2), then patient will be instructed to discontinue blood glucose monitoring.

4.2.6.4.1 If the patient does have a "*concerning toxicity*" or "*serious toxicity*" they must discontinue their investigational medication (see section 5.3.2) and thus can also discontinue with fingerstick glucose draws.

4.2.6.5 Documentation of corticosteroid use (record the date of initiation, dose and reason for initiation of any new corticosteroid, especially dexamethasone).

4.2.7 1 month after SRS (- 5 or + 10 days)

4.2.7.1 Discontinue investigational medication (last dose is taken the evening of obtaining the follow-up MRI). Have patient return all remaining (untaken) investigational medication tablets.

4.2.7.2 Follow-up brain MRI with and without contrast. T1-weighted, T2, and/or FLAIR MRI of the brain (maximum slice thickness 5mm). FLAIR imaging is preferred.

4.2.7.2.1 T1 post gadolinium sequence will be imported into the Eclipse treatment planning system and the radiation oncologist (who will be blinded to the patient's investigational medication) will contour the enhancing tumor that received the prescribed dose of SRS.

4.2.7.2.2 FLAIR sequence will be imported into the Eclipse treatment planning system. FLAIR volume will be automatically calculated using "Region Growing" on Eclipse (Appendix I). The automated contours will be verified and modified as needed by the radiation oncologist who will be blinded to the patient's investigational medication.

4.2.7.3 Follow-up history and physical with neurologic examination and corticosteroid use documentation (record the date of initiation, dose and reason for initiation of any new corticosteroid, especially dexamethasone). A last fingerstick glucose draw will be done by the nurse/research team member.

4.1.7.4 Review and collect the patient's blood glucose and medication administration logs.

4.2.7.5 Adverse event evaluation.

4.2.7.6 CBC with differential and CMP including LFTs.

4.2.8 3 months after SRS (- 10 or + 14 days)

4.2.8.1 Follow-up brain MRI with and without contrast. T1-weighted, T2, and/or FLAIR MRI of the brain (maximum slice thickness 5mm). FLAIR imaging is preferred.

4.2.8.1.1 T1 post gadolinium sequence will be imported into the Eclipse treatment planning system and the radiation oncologist (who will be blinded to the patient's investigational medication) will contour the enhancing tumor that received the prescribed dose of SRS.

4.2.8.1.2 FLAIR sequence will be imported into the Eclipse treatment planning system. FLAIR volume will be automatically calculated using "Region Growing" on Eclipse (Appendix I). The automated contours will be verified and modified as needed by the radiation oncologist who will be blinded to the patient's investigational medication.

4.2.8.2 Follow-up history and physical with neurologic examination and corticosteroid use documentation (record the date of initiation, dose and reason for initiation of any new corticosteroid, especially dexamethasone).

4.2.8.3 Adverse event evaluation.

4.2.8.4 CBC with differential and CMP including LFTs.

4.2.9 Conditions for early patient stopping of investigational medication

4.2.9.1 A dose limiting toxicity (DLT) is reached. See section 5.3.2.

4.2.9.2 Patient requires corticosteroid administration after registration but prior to SRS, please note these patients will be deemed inevaluable.

5.0 STUDY DESIGN AND TREATMENT SUMMARY

Please see the Treatment Schema on pages 3-4 for detailed diagrams. Due to COVID-19, these study procedures may be conducted remotely, if necessary.

5.1 Pilot Portion

10 evaluable patients will be enrolled onto the Pilot Portion. Should there be a glyburide dose reduction, 10 evaluable patients at this lower glyburide dose must be assessed. Inevaluable patients will be replaced.

Patients with brain metastases, who are not taking dexamethasone (or any other corticosteroid with the purpose of treating cerebral edema) within 5 days prior to SRS, after informed consent, will be treated with:

1. Non-Micronized glyburide (1.25 mg orally twice a day (po BID)) should begin5 days prior to SRS to be taken until the evening dose on the day of the one month follow-up MRI.
2. Radiosurgery will be linac-based and must be initiated at least 5 days after starting glyburide (can be more for patients being treated with linac-based radiosurgery where the MRI may be done within 21 days prior to SRS treatment).

For treatment planning and at the time of the one and three month follow-up appointments, the patient must undergo a brain MRI with and without contrast. T1-weighted, T2, and/or FLAIR MRI of the brain (maximum slice thickness 5mm). FLAIR imaging is preferred. The treatment planning MRI may be done within 21 days prior to SRS treatment only for patients being treated with linac-based radiosurgery where it is not standard of care to complete a MRI on the day of SRS (as it is with gamma knife).

T1 post-gadolinium sequences and FLAIR axial sequences from the treatment planning MRI (see note above regarding linac-based radiosurgery patients) and at the one and three month follow-up appointments will be imported into the Eclipse treatment planning system. On the T1 post gadolinium sequences, the radiation oncologist will contour the enhancing tumor that received the prescribed dose of SRS. Using the FLAIR sequences Eclipse will automatically calculate FLAIR volume using "Region Growing" (Appendix I). The automated contours will be verified and modified as needed by the radiation oncologist.

5.1.1 Patients can only be enrolled after all eligibility criteria are met. The date of registration/enrollment/study entry is considered to be the day the Eligibility Checklist is signed by the verifying physician and should be no later than 5-9 days prior to SRS. Once a patient is enrolled, a unique case number will be assigned.

5.2 Randomized Portion

The Randomized Portion of this study will only proceed if there have been 10 evaluable patients on the Pilot Portion (this includes both full dose glyburide and reduced dose glyburide, if applicable) and it is deemed safe. All data will be reviewed and approved by the Data Safety Monitoring/Quality Assurance Committee (DSMQAC) after the Pilot Portion and prior to starting the Randomized Portion at the safe dose as determined by the Pilot Portion. The Randomized Portion will enroll 40 evaluable patients. Inevaluable patients will be replaced.

Patients with brain metastases, who are not taking dexamethasone (or any other corticosteroid with the purpose of treating cerebral edema) within 5 days prior to SRS, after informed consent, will be randomized to a blinded investigational medication:

- Non-Micronized glyburide (1.25 mg po BID) should begin at least 5 days prior to SRS to be taken until the evening dose on the day of the one month follow-up MRI.
  OR
- Placebo (1 tablet po BID) should begin at least 5 days prior to SRS to be taken until the evening dose on the day of one month follow-up MRI.

All patients will receive linac-based radiosurgery, which must be initiated at least 5 days after starting the investigational medication (can be more for patients being treated with linac-based radiosurgery where the MRI may be done within 21 days prior to SRS treatment).

For treatment planning and at the time of the one and three month follow-up appointments, the patient must undergo a brain MRI with and without contrast. T1-weighted, T2, and/or

FLAIR MRI of the brain (maximum slice thickness 5mm). FLAIR imaging is preferred. The treatment planning MRI may be done within 21 days prior to SRS treatment only for patients being treated with linac-based radiosurgery where it is not standard of care to complete a MRI on the day of SRS (as it is with gamma knife).

T1 post-gadolinium sequences and FLAIR axial sequences from the treatment planning MRI (see note above regarding linac-based radiosurgery patients) and at the one and three month follow-up appointments will be imported into the Eclipse treatment planning system. On the T1 post gadolinium sequences, the radiation oncologist will contour the enhancing tumor that received the prescribed dose of SRS. Using the FLAIR sequences Eclipse will automatically calculate FLAIR volume using "Region Growing" (Appendix I). The automated contours will be verified and modified as needed by the radiation oncologist. Physicians, patients, and the study team will be blinded to the patient's investigational medication.

5.2.1 Patients can only be enrolled after all eligibility criteria are met. The date of registration/enrollment/study entry is considered to be the day the Eligibility Checklist is signed by the verifying physician and should be no later than 5-9 days prior to SRS. Once a patient is enrolled, a unique case number will be assigned to the patient and blinded randomization will occur. Patients will be randomized by the UAB Investigational Drug Services (IDS) Pharmacy, who will hold the blind for this study.

5.3 Definition of Dose Limiting Toxicity (DLT)

5.3.1 Pilot Portion

All adverse events and toxicities will be graded and reported according to the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The CTCAE version 4.0 is located on the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. See Appendix VII for Adverse Event (AE) definitions and grading scale information.
If multiple toxicities are seen, the presence of a DLT should be based on the most severe toxicity experienced. Any patient who achieves a DLT will be taken off of glyburide immediately, but will still be evaluable.

Concerning Toxicity

1. Any **asymptomatic grade 3 or 4 hypoglycemia** as defined by CTCAE version 4.0.
2. Any **non-hematologic grade 3 or greater toxicity** (including neurologic toxicity) that is associated with a blood glucose level ≤ 80 mg/dl and is resolved with "low blood sugar intervention" (e.g. a return of blood glucose level to ≥ 80 mg/dl). **See Section 5.4.1.1 for a List of Low Blood Sugar Interventions.**

Serious Toxicity

1. Any **grade 5 toxicity** that is deemed by the investigator to be **at least possibly attributable to glyburide.**
2. Any **symptomatic grade 3 or 4 hypoglycemia associated with a non-hematologic grade 3 or greater toxicity** that is not resolved with "low blood sugar intervention" (e.g. does not

return to blood glucose level to ≥ 80 mg/dl) that is deemed by the investigator to be at least possibly attributable to glyburide. **See Section 5.4.1.1 for a List of Low Blood Sugar Interventions.**

Glyburide will be discontinued for any patient that meets the criteria for either a **"*concerning toxicity*"** or **"*serious toxicity*".** These patients will still be evaluable.

Any **"*concerning toxicity*"** that is observed in at least 6 (of 10 evaluable) patients will trigger a dose reduction (see section 7.1). After 1 dose reduction, if at least 6 (of 10 evaluable) patients are observed to have a **"*concerning toxicity*",** the study will be terminated.

Any **"*serious toxicity*"** that is observed in at least 1 (of 10 evaluable) patients will trigger a dose reduction. After 1 dose reduction, if at least 1 (of 10 evaluable) patients is observed to have a **"*serious toxicity*",** the study will be terminated.

5.3.1.1 If a dose reduction should occur, it will occur once the pre-specified DLT is reached. Glyburide will be reduced to 0.75 mg po BID. In the event this dose reduction should occur, the Pilot Portion will be performed using the reduced dose (e.g. 10 evaluable patients are required to be assessed). If another DLT is observed at the reduced glyburide dose warranting a dose reduction, the study will be terminated.

5.3.1.2 The patient who experiences a DLT (e.g. either a "*concerning toxicity*" or "*serious toxicity*") will stop glyburide immediately, but will still be evaluable. If the DLT is a "*concerning toxicity*", all other patients currently on treatment at the time may continue at their current glyburide dose. If the DLT is a "*serious toxicity*", all other patients currently on treatment will either be dose reduced immediately (if on full dose glyburide) or stop glyburide immediately (if on reduced dose glyburide). All other patients will still be evaluable.

5.3.2 <u>Randomized Portion</u>

All adverse events and toxicities will be graded and reported according to the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The CTCAE version 4.0 is located on the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. See Appendix VII for Adverse Event (AE) definitions and grading scale information.
If multiple toxicities are seen, the presence of a DLT should be based on the most severe toxicity experienced. Any patient who achieves a DLT will be taken off of the investigational medication immediately, but will still be evaluable.

<u>Concerning Toxicity</u>

1. Any **asymptomatic grade 3 or 4 hypoglycemia** as defined by CTCAE version 4.0.
2. Any **non-hematologic grade 3 or greater toxicity** (including neurologic toxicity) that is associated with a blood glucose level ≤ 80 mg/dl and is resolved with "low blood sugar intervention" (e.g. a return of blood glucose level to ≥ 80 mg/dl).

Serious Toxicity

1. Any **grade 5 toxicity** that is deemed by the investigator to be **at least possibly attributable to the investigational medication.**
2. Any **symptomatic grade 3 or 4 hypoglycemia** that is associated with a **non-hematologic grade 3 or greater toxicity** that is not resolved with "low blood sugar intervention" (e.g. does not return to blood glucose level of ≥ 80 mg/dl) that is deemed by the investigator to be **at least possibly attributable to the investigational mediation**.

Investigational medication will be discontinued for any patient that meets the criteria for a "*concerning toxicity*" or "*serious toxicity*". These patients will still be evaluable. All other patients currently on treatment at the time may continue with their current investigational medication without interruption.

5.4 Safety and efficacy (blood glucose monitoring)

5.4.1 Pilot Portion

All patients will be provided with a medication/blood glucose log, a blood glucose monitor, and taught to perform self fingerstick glucose draws (see Appendices II-VI). The first blood glucose draw will be done by a nurse or research team member on the visit 5-9 days prior to SRS and the initial value will be recorded in the blood glucose log. Starting at the initiation of glyburide and for at least the first week after SRS, the patient will take and record blood glucose levels 4 times a day (in the morning before breakfast [fasting], before lunch, before dinner, and before bed). After one week post SRS, if the patient does not experience a dose limiting toxicity (DLT, as defined in section 5.3.1), he/she will be instructed to obtain blood glucose levels once a day (in the morning before breakfast [fasting]) until the discontinuation of glyburide. If the patient does experience a DLT then he/she must discontinue glyburide (as per section 5.3.1) and will not have to continue checking their blood glucose levels.

If the patient is symptomatic and this is thought to be attributable to hypoglycemia, he/she should check a fingerstick glucose level and begin "low blood sugar intervention" as described in **Section 5.4.1.1** (also see Appendix IV). If fingerstick glucose levels reach ≤ 80 mg/dl (symptomatic or asymptomatic), the patient should begin "low blood sugar intervention". If "low blood sugar intervention" does not cause the blood sugar to rise above 80 mg/dl, or if symptoms persist, the patient will be instructed to contact the study team and/or call 911 for emergency services.

5.4.1.1 "Low Blood Sugar Intervention":

Procedures:

1. Take 15 grams of carbohydrate:
    a. 3 or 4 glucose tablets or
    b. 4 oz (1/2 cup) of fruit juice or
    c. 6 oz regular soda (about 1/2 can)
2. Rest and wait 15 minutes
3. Recheck blood sugar

4. Repeat Steps 1-3 if blood sugar still less than 80 mg/dl
5. If next meal is more than 1 hour away, eat a snack.

5.4.2 Randomized Portion

5.4.2.1 All patients will be provided with a medication/blood glucose log, a blood glucose monitor, and taught to perform self fingerstick glucose draws (see Appendices II-VI). The first blood glucose draw will be done by a nurse or research team member on the visit 5-9 days prior to SRS and the initial value will be recorded in the blood glucose log.

5.4.2.2 If the Pilot Portion (at either full dose or at one dose reduction) demonstrates no "***serious toxicities***" and ≤ 3 "***concerning toxicities***" (described in section 5.3.1), patients in the Randomized Portion of the trial will be taught and instructed to measure blood glucose levels once a day (in the morning before breakfast (fasting)) starting at the initiation of the investigational medication and continuing for at least the first week after SRS. If no "***concerning toxicities***" or "***serious toxicities***" are found at the one week post SRS visit, then the patient may proceed through the rest of the trial with no further need to assess blood glucose via the fingerstick draws. If the patient does experience a "***concerning toxicity***" or "***serious toxicity***" then he/she must discontinue their investigational medication (as per section 5.3.2) and will not have to continue checking their blood glucose levels.

5.4.2.3 If the Pilot Portion (at either full dose or at one dose reduction) demonstrates no "***serious toxicities***" and 4-5 "***concerning toxicities***" (described in section 5.3.1), patients in the Randomized Portion of the trial will be taught and instructed to measure blood glucose as per section 5.4.1.

5.5 Radiation Therapy

The radiation dose range is 18-24 Gy in a single fraction or 25-30Gy in 5 fractions for patients with a total tumor volume ≤ 10 cm^3 and 15-22 Gy in a single fraction for 25-30Gy in 5 fractions for a total tumor volume > 10 cm^3 (14).

For brain stem lesions treated in a single fraction, the following dosing may be followed:

- Tumor volume of 0-1 cm^3 = dose range of 18-20 Gy
- Tumor volume of > 1 - 4 cm^3 = dose range of 16-18 Gy
- Tumor volume of > 4 cm^3 = dose range of 14-15 Gy

5.6 Treatment Calendar

Please see Appendix VIII: Study Schedule of Events for further details.

6.0 RADIATION THERAPY

6.1 Timing of Radiation Therapy

Stereotactic radiosurgery (SRS) should be delivered at least 5 days after initiating the glyburide (Pilot Portion) or investigational medication (Randomized Portion).

It is possible at the time of SRS/MRI for treatment planning that one of these scenarios occurs in which the patient should be removed from the protocol (thus making the patient inevaluable):

1. An identified metastasis at the time of registration now exceeds the acceptable upper limit diameter are visualized. Any such lesion should not be treated with SRS and the patient should be removed from the protocol.
2. If the lesions are not visualized, radiosurgery should not be delivered and the patient should be removed from the protocol.
3. If patient is unable to proceed with SRS for any reason (such as claustrophobia, location of lesion and head anatomy make treatment physically impossible, etc.), SRS should not be delivered and the patient should be removed from the protocol.

6.2 Technical Factors

Treatment shall be delivered with linac-based radiosurgery machines. A treatment planning system capable of generating isodose distributions in three dimensions for a given treatment is required.

6.3 Localization, Simulation, and Immobilization

All institutions must use FDA-approved stereotactic localization procedures for imaging and treatment delivery. MRI may be performed within 21 days prior to SRS treatment and can be fused with CT done at the time of simulation [treatment planning] for linac-based radiosurgery per standard institutional guidelines. Intravenous gadolinium administration is required for the MRI.

Stereotactic MRI slice thickness may not exceed 5 mm.

6.4 Treatment Planning

6.4.1 Total Dose Determination

The total dose should be 18-24 Gy for tumors < 2cm in diameter and 15-22 Gy for tumors > 2cm in diameter.

Alternatively, a 5 fraction radiosurgery plan using 25Gy in 5 fractions or 30Gy in 5 fractions may be utilized.

6.4.2 Dose Prescription

The minimum dose shall be established by the SRS treatment planning software or by an examination of the dose distribution on each axial level on which the target volume has been defined, and/or by the target dose-volume histogram.

6.4.3 Dose Limitation to Critical Structures

Single fraction plans: The maximum dose to the Optic Nerve and Chiasm should not exceed 10Gy (point dose up to 12 gy is allowed). The brainstem max is generally kept to a max of 12.5Gy. This volume may be allowed to exceed this to up to 16 Gy to a point dose. All radiosurgery plans will be peer reviewed for safety.

Five fraction plans: The maximum dose to the Optic Nerve and Chiasm should not exceed 25Gy (point dose up to 30 gy is allowed). The brainstem max is generally kept to a max of 31Gy. This volume may be allowed to exceed this to up to 35 Gy to a point dose. All radiosurgery plans will be peer reviewed for safety.

6.4.4 Target Volume

The target volume will include the enhancing portion of the metastatic lesions. Surrounding areas of edema will not be considered part of the target volume.

6.5 Radiosurgery Treatment Planning Data

6.5.1 Isodose distributions must be calculated, and the prescription isodose line clearly designated, for each target lesion in the transverse, coronal, and sagittal planes.

6.5.2 The isodose distributions on the required three planes for each target lesion will include isodose lines (in % dose) that represent 10% dose increments.

6.6 Treatment Planning Goals

6.6.1 Target Coverage QA

6.6.1.1 *Per protocol*: The submitted 90% isodose line (90% of the prescription dose, not total dose) completely encompasses target.

6.6.1.2 *Acceptable variation*: 80% isodose line covers the target.

6.6.1.3 *Unacceptable deviation*: 80% isodose line does not cover target.

6.6.2 Dose Homogeneity QA

The ratio of the maximum dose to the prescribed dose (MD/PD) is:

6.6.2.1 *Per protocol* if ≤ 2.

6.6.2.2 *Acceptable variation* if > 2 but ≤ 2.5.

6.6.2.3 *Unacceptable deviation* if > 2.5.

7.0 DRUG THERAPY

7.1 Pilot Portion

7.1.1 Non-Micronized glyburide (1.25 mg po BID) should be administered orally twice a day beginning at least 5 days prior to SRS. Glyburide will be taken in the morning with breakfast and in the evening with dinner. All patients on the Pilot Portion of the study will receive glyburide which will continue until the evening dose on the day of one month post SRS follow-up MRI. If the patient misses a dose at any time, it will not be made up. All doses (whether missed or taken) should be recorded in the medication administration log.

7.1.2 In the event of a DLT between the time of glyburide initiation and the time of the one month follow-up MRI at full dose glyburide, one dose reduction will take place (the dose reduction will be immediate if there is one patient with a "*serious toxicity*", but a full analysis may be required to determine if there are 6 or more patients with "*concerning toxicities*" which would warrant a dose reduction). The patient who experienced the DLT will stop glyburide

immediately. If the DLT was a "*concerning toxicity*", all other patients currently on treatment at the time may continue at their current full dose glyburide. If the DLT was a "*serious toxicity",* all other patients currently on treatment will be dose reduced immediately.

7.1.2.1 For patients who have already begun glyburide and require an immediate dose reduction, the full dose glyburide tablets will be returned to the study team and in turn to the UAB Investigational Drug Services (IDS) pharmacy. Subsequently 0.75 mg non-micronized glyburide will be dispensed to the patient and administered orally twice a day (in the morning with breakfast and in the evening with dinner) until the evening dose on the day of one month follow-up MRI.

7.1.3 In the event of a DLT on the reduced dose of glyburide, the trial will be terminated. The termination could be immediate if there is one patient with a "*serious toxicity",* but a full analysis may be required to determine if there are 6 or more patients with "*concerning toxicities*" which would warrant study termination. The patient who experienced the DLT will stop glyburide immediately. If the DLT is a "*concerning toxicity*", all other patients currently on treatment at the time may continue at their current dose reduced glyburide. If the DLT is a "*serious toxicity*", all other patients currently on treatment will stop glyburide immediately.

7.1.4 If a patient suffers a DLT (either a "*concerning toxicity*" or a "*serious toxicity*") after registration but before SRS, he/she will be removed from the protocol and considered inevaluable.

7.2 Randomized Portion

7.2.1 Non-Micronized glyburide (1.25 mg po BID) or placebo (1 tablet po BID) should be administered orally twice a day beginning at least 5 days prior to SRS. The investigational medication will be taken in the morning with breakfast and in the evening with dinner. All patients and the study team will be blinded to the investigational medication which will continue until the evening dose on the day of the one month post SRS follow-up MRI. If the patient misses a dose at any time, it will not be made up. All doses (whether missed or taken) should be recorded in the medication administration log.

7.2.1.1 In the event of a DLT in the Pilot Portion requiring a dose reduction and this dose is considered safe, patients will receive either a reduced dose of non-micronized glyburide (now at 0.75 mg po BID) or the placebo (1 tablet po BID). The investigational medication will be taken in the morning with breakfast and in the evening with dinner. All patients and the study team will be blinded to the investigational medication which will continue until the evening dose on the day of the one month post SRS follow-up MRI. If the patient misses a dose at any time, it will not be made up. All doses (whether missed or taken) should be recorded in the medication administration log.

7.2.2 In the event of a DLT in the Randomized Portion of the study, the patient who experienced the DLT will stop their investigational medication immediately. Other patients currently on study at the time of the DLT will continue on study treatment without interruption**.**

7.2.3 If a patient suffers a DLT (either a "*concerning toxicity"* or a "*serious toxicity*") after registration but before SRS, he/she will be removed from the protocol and considered inevaluable.

7.3 Data Safety Monitoring and Adverse Events

7.3.1 Data and Safety Monitoring / Quality Assurance Committee

This study will follow the UAB Data and Safety Monitoring Plan maintained by the UAB Comprehensive Cancer Center. This includes monthly reporting to the Clinical Trial Monitoring Committee for all adverse events. Serious adverse events are also reported to the UAB IRB and the study PI within 24 hours.

7.3.2 Anticipated Toxicities

All anticipated toxicities are listed in the informed consent document.

7.3.3 Toxicity Reporting

The research team and the treating physicians/Principal Investigator will review the toxicities and record them in OnCore. Attribution of toxicity to protocol and clinical relevance will be reviewed.

If a dose limiting toxicity (DLT) or other significant medical event is unexpected and probably related to study treatment, then it will be submitted to the UAB IRB via the Problem Report form. All adverse events entered into OnCore will be submitted for review on an annual basis.

Patients that are withdrawn from the study after beginning protocol treatment will be followed for adverse events for 30 days after last dose of glyburide or investigational medication.

7.3.4 Grading Toxicities and Adverse Events

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting on this study. The CTCAE version 4.0 is located on the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. See Appendix VII for Adverse Event (AE) definitions and grading scale information.

PILOT PORTION

If multiple toxicities are seen, the presence of a DLT should be based on the most severe toxicity experienced. Any patient who achieves a DLT will be taken off of glyburide immediately, but will still be evaluable.

Concerning Toxicity

1. Any asymptomatic grade 3 or 4 hypoglycemia as defined by CTCAE version 4.0.
2. Any non-hematologic grade 3 or greater toxicity (including neurologic toxicity) that is associated with a blood glucose level ≤ 80 mg/dl and is resolved with "low blood

sugar intervention" (e.g. a return of blood glucose level to ≥ 80 mg/dl). See **Section 5.4.1.1 for a List of Low Blood Sugar Interventions**.

Serious Toxicity

3. Any grade 5 toxicity that is deemed by the investigator to be at least possibly attributable to glyburide.
4. Any symptomatic grade 3 or 4 hypoglycemia associated with a non-hematologic grade 3 or greater toxicity that is not resolved with "low blood sugar intervention" (e.g. does not return to blood glucose level to ≥ 80 mg/dl) that is deemed by the investigator to be at least possibly attributable to glyburide. **See Section 5.4.1.1 for a List of Low Blood Sugar Interventions**.

Glyburide will be discontinued for any patient that meets the criteria for either a **"*concerning toxicity*" or "*serious toxicity*".** These patients will still be evaluable.

Any **"*concerning toxicity*"** that is observed in at least 6 (of 10 evaluable) patients will trigger a dose reduction (see section 7.1). After 1 dose reduction, if at least 6 (of 10 evaluable) patients are observed to have a **"*concerning toxicity*",** the study will be terminated.

Any **"*serious toxicity*"** that is observed in at least 1 (of 10 evaluable) patients will trigger a dose reduction. After 1 dose reduction, if at least 1 (of 10 evaluable) patients is observed to have a **"*serious toxicity*",** the study will be terminated.

RANDOMIZED PORTION

If multiple toxicities are seen, the presence of a DLT should be based on the most severe toxicity experienced. Any patient who achieves a DLT will be taken off of the investigational medication immediately, but will still be evaluable.

Concerning Toxicity

1. Any asymptomatic grade 3 or 4 hypoglycemia as defined by CTCAE version 4.0
2. Any non-hematologic grade 3 or greater toxicity (including neurologic toxicity) that is associated with a blood glucose level ≤ 80 mg/dl and is resolved with "low blood sugar intervention" (e.g. a return of blood glucose level to ≥ 80 mg/dl).**See Section 5.4.1.1 for a List of Low Blood Sugar Interventions.**

Serious Toxicity

3. Any grade 5 toxicity that is deemed by the investigator to be at least possibly attributable to the investigational medication.
4. Any symptomatic grade 3 or 4 hypoglycemia that is associated with a non-hematologic grade 3 or greater toxicity that is not resolved with "low blood sugar intervention" (e.g. does not return to blood glucose level of ≥ 80 mg/dl) that is deemed by the investigator to be at least possibly attributable to the investigational mediation. **See Section 5.4.1.1 for a List of Low Blood Sugar Interventions.**

Investigational medication will be discontinued for any patient that meets the criteria for a **"*concerning toxicity*" or "*serious toxicity*".** These patients will still be evaluable. All other patients currently on treatment at the time may continue with their current investigational medication without interruption.

7.4 Drug/Placebo Supply and Ordering

This protocol will use the Investigational Drug Services (IDS) pharmacy at UAB. The IDS pharmacy will be the only people unblinded to the study's investigational medication for the Randomized Portion of the study. The rest of the study team including treating physicians and patients will be blinded to the investigational medication.

Glyburide and the placebo will both be available by commercial/generic supply. Please note the placebo pill is not a sugar pill.

IDS will hold a supply of glyburide and placebo and dispense as appropriate when patients are enrolled on study. Once a patient is enrolled, a prescription for either glyburide or investigational medication will be faxed to the IDS pharmacy. Once the investigator has been verified by IDS, the drug will be dispensed. A sufficient supply of glyburide or investigational medication will be dispensed for the patient's entire study participation (beginning at least 5 days prior to SRS and continuing till the evening dose of the one month post SRS MRI scan). The investigational medication, when dispensed, will be packaged in a way that will keep the study team and patient blinded (for the Randomized Portion of the study). Once prepared by the IDS pharmacy the research team will be notified to retrieve the glyburide or investigational medication supply and take it to the patient.

7.4.1 In the event that a dose reduction is required for a patient who is currently on treatment in the Pilot Portion of the study (see Section 7.1) the following will occur. The patient will be notified and asked to return their supply of glyburide immediately. The IDS pharmacy will appropriately catalog (and if applicable destroy) the tablets per institutional guidelines. 0.75 mg glyburide tablets will then be dispensed for the patient. The study team will retrieve the new dose reduced supply of glyburide and provide it to the patient. Further dispensing of glyburide will be at this reduced dose by IDS unless otherwise notified by the study team.

7.5 Initiation of Therapy

All patients that are registered on study and eligible to receive therapy should initiate drug therapy (glyburide on the Pilot Portion or investigational medication on the Randomized Portion) at least 5 days prior to SRS.

7.6 Guidelines and Procedure for Unblinding Treatment (Randomized Portion)

The site/treating physician may request to unblind their patient's treatment randomization only under specific circumstances. All must be done to ensure the blind. The following circumstances would be deemed appropriate for unblinding:

- A life-threatening event or extraordinary clinical circumstance in which knowledge of the drug assignment will affect clinical judgment.

7.6.1 The unblinding procedure is outlined below. All parties must strictly adhere to the procedure in order to maintain protocol integrity and protect the blind.

1. The requesting physician will call and/or email the research team to request the unblinding of their patient.
2. The requesting physician will provide the case number, reason and appropriate details for the request of unblinding.
3. The research team will then determine after consulting with the PI of the study if unblinding is appropriate in the specific case addressed. If unblinding is denied, the reason will be provided in a timely fashion to the requesting physician. An appeal can be made by the requesting physician if appropriate.
4. If approved for unblinding, the IDS pharmacy is contacted by the research team.
5. The IDS pharmacy may be in direct contact with the requesting physician or the research team/PI may be asked to relay the unblinded information to the requesting physician.

All discussions and outcomes of a blinding request will be well documented in the patient's chart as well as in the research office. All research staff involved in the unblinding activity for this protocol should continue to remain blinded to drug assignment/randomization if possible.

7.6.2 The research office will notify the UAB IRB and UAB Clinical Trials Monitoring Committee (CTMC) of patient unblindings at the time of the annual protocol review. If appropriate and fitting the criteria of the Problem Report form, appropriate steps will be taken for reporting.

7.6.3 Unblinded patients will be taken off study treatment and followed for 30 days after last dose of investigational medication, irrelevant to the date of unblinding.

8.0 SURGERY AND OTHER THERAPY

Intracranial surgery is not permitted on this study unless the intracranial surgical resection is of a lesion that leaves other intact lesions to be targeted with SRS and this surgery is completed prior to initiating glyburide or the investigational medication (which will be at least 5 days prior to SRS). There will be no SRS boost to the tumor bed of a resected lesion allowed. Extracranial surgery is permitted during the study at the discretion of the treating team.

8.1 Permitted Supportive Therapy

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented in each site's patient charts as concomitant medication.

8.1.1 Anticonvulsants: Anticonvulsants may be used as clinically indicated. Doses at study entry and at specific time points of the treatment must be recorded.

8.1.2 Antiemetics: Prophylactic antiemetics may be administered at the treating physician's discretion.

8.1.3 Cytotoxic chemotherapy is permitted at the discretion of the treating physician(s).

8.1.4 All further therapy that is not included in Section 8.2 is permitted at the treating physician's discretion, but should be recorded.

8.2 Non-Permitted Supportive Therapy

8.2.1 Corticosteroids: Dexamethasone (or any other corticosteroid whose purpose is to treat cerebral edema) should only be administered if the patient is clinically symptomatic, has imaging demonstrating increasing cerebral edema, and is deemed by the treating physician to require dexamethasone (or another corticosteroid). If administered between SRS and the one month follow-up MRI, these patients will be recorded as a treatment failure (primary endpoint). If initiated prior to SRS, this is criteria for withdrawal from the protocol, these patients would be deemed inevaluable. If initiated after the one month follow-up MRI, the dose, value, and reason will be recorded. Low dose prednisone or other non-dexamethasone steroids are allowed as long as they are not administered with the intent of treating cerebral edema.

8.3 Imaging

8.3.1 All patients must have a contrast enhanced MRI within 60 days of study entry.

8.3.2 Pre-treatment tumor/edema ratio should be determined by importing the pretreatment MRI into the Eclipse treatment planning system. MRI with and without contrast.T1-weighted, T2 and/or FLAIR MRI of the brain (maximum slice thickness 5mm). FLAIR imaging is preferred. The total volume of tumor and total volume of edema should be recorded. If the ratio of edema/tumor volume is ≥ 35:1, this will be counted as a risk factor for entering the trial on the Randomized Portion.

8.3.3 MRI obtained at the time of SRS (for treatment planning; may be within 21 prior to SRS treatment for patients being treated with linac-based radiosurgery where it is not standard of care to complete a MRI on the day of SRS [as it is with gamma knife]), at the time of the one month follow-up visit, and at the time of the 3 month follow-up visit must be taken with a MRI machine. These studies must all employ MRI with and without contrast. T1-weighted, T2 and/or FLAIR MRI of the brain (maximum slice thickness 5mm). FLAIR imaging is preferred.

8.3.4 FLAIR sequences at time of SRS (see note above regarding linac-based radiosurgery patients), one month follow-up, and 3 month follow-up MRI scans will be imported into the Eclipse treatment planning system where FLAIR volume will be automatically calculated using "Region Growing" on Eclipse (Appendix I). The automated contours will be verified and modified as needed by the radiation oncologist. Physicians, patients, and the study team will be blinded to the patient's investigational medication on the Randomized Portion. The primary endpoint of the Randomized Portion will constitute a mean of the edema values as measured by the region growing tool and verified and modified as needed by the radiation oncologist (see Appendix I).

8.3.5 T1 post gadolinium sequences at time of SRS (see note above regarding linac-based radiosurgery patients), one month follow-up, and 3 month follow-up MRI scans will be imported into the Eclipse treatment planning system where the enhancing tumor(s) that was treated with the full dose of SRS will be manually contoured by the radiation oncologist who will be blinded to patient's investigational medication on the Randomized Portion.

8.4 Definition of Edema Volume

8.4.1 Absolute edema volume will be calculated by subtracting the tumor volume as contoured on the T1 post gadolinium sequences (see Section 8.3.5) from the FLAIR edema volume (see Section 8.3.4).

8.4.2 Absolute edema will be independently verified and modified as needed by the radiation oncologist.

8.4.3 Absolute edema ≤ 1.00 cc will not be considered edema (defined as no edema).

8.4.4 Patients will be considered to have edema increase if an absolute edema increase is ≥ 5.0% (this is an absolute percentage) from the time of SRS (see note above regarding linac-based radiosurgery patients) to the time of the one month follow-up MRI.

8.4.5 Patients with no edema at time of SRS (see note above regarding linac-based radiosurgery patients) who achieve an absolute edema value of > 1.00 cc at the time of the one month follow-up MRI will be considered to have an edema increase.

8.4.6 Primary endpoint of the Randomized Portion is edema increase as defined in Sections 8.4.4 and 8.4.5.

9.0 STATISTICAL CONSIDERATIONS

9.1 Definition of primary outcome/endpoint

9.1.1 Pilot Portion: Occurrence of Dose Limiting Toxicities (DLTs) between the time of glyburide initiation and the time of the one month follow-up MRI.

9.1.2 Randomized Portion:

Each eligible patient will be evaluated for treatment outcome as success or failure, as defined later in this section. Each patient's treatment outcome will be associated with randomized regimen regardless of the treatment the patient actually receives. A treatment failure will be considered to have occurred if edema increases sufficiently to require the initiation of dexamethasone (or any corticosteroid administration with the purpose of treating cerebral edema) between the time of SRS* and the time of the one month follow-up MRI, or the patient dies in that same interval from a cause considered probably or likely related to Glyburide. Otherwise, the patient will be considered to have experienced treatment success.

9.2 Definition of secondary outcomes/endpoints

9.2.1 Pilot Portion

1. Time until dexamethasone initiation (or any corticosteroid administration with the purpose of treating cerebral edema) as measured between the time of SRS* and the time of the one and three month post SRS MRI scans.
2. Incidence of CTCAE version 4.0 reportable toxicities of grades 2-5.

3. Incidence of CTCAE version 4.0 reportable toxicities of grades 1-2 Cardiac Disorders or Hepatobiliary Disorders.
4. Cerebral edema increase as measured on FLAIR volumetric imaging, defined from MRI taken at the time of SRS* and the time of the one and three month post SRS MRI scans.
5. Absolute volume change of index tumor(s) that received radiosurgery as manually contoured by the radiation oncologist defined from T1 post gadolinium sequences at the time of SRS* and the time of the one and three month post SRS MRI scans.

9.2.2 Randomized Portion

1. Dexamethasone initiation (or any corticosteroid administration with the purpose of treating cerebral edema) between the treatment groups (as measured between the time of SRS* and the time of the one and three month post SRS MRI scans).
2. Rate of CTCAE version 4.0 grade 2-5 Nervous system disorder toxicities between the treatment groups.
3. Rate of CTCAE version 4.0 grade 1-5 Cardiac Disorders and Hepatobiliary Disorders between the treatment groups.
4. Comparison of mean rate of cerebral edema increase as measured on FLAIR volumetric imaging between the treatment groups (defined from MRI taken at the time of SRS* and the time of the one and three month post SRS MRI scans).
5. Comparison of median absolute volume change of index tumor(s) that received radiosurgery as manually contoured by the radiation oncologist between the treatment groups (defined from T1 post gadolinium image at the time of SRS* and the time of the one and three month post SRS MRI scans).

* Please note that the MRI may be performed within 21 days prior to SRS treatment only if the patient is being treated with linac-based radiosurgery and it is not standard of care to complete a MRI on the day of SRS (as it is with gamma knife).

9.3 Analytic plan for primary objective

9.3.1 Pilot Portion: Each evaluable patient will be assessed for "*concerning toxicities*" and "*serious toxicities*". If 6 or more patients demonstrate a "*concerning toxicity*" or 1 or more patients experience a "*serious toxicity*", the therapy will be considered not feasible to deliver and one dose reduction will occur. If 6 or more patients demonstrate a "*concerning toxicity*" or 1 or more patients experience a "*serious toxicity*" on the dose reduced schedule, the intervention will be considered too toxic and the protocol will be terminated. Inevaluable patients will be replaced.

9.3.2 Randomized Portion:

After the acceptable glyburide dose has been established, the randomized portion will commence. No formal interim monitoring will take place and study analysis will be done when all 20 randomized patients are accrued in each treatment regimen. The results from this portion of the trial will be used as a screening mechanism for assessing whether glyburide should be studied in a formal randomized trial. The number of patients who experience treatment successes will be compared between the two regimens using the

exact test of proportions. If this test yields a one-sided test of equality of proportions of treatment success obtains a p-value of 0.30 or less, glyburide treatment will be considered as sufficiently interesting for further study. Otherwise, glyburide will be considered not interesting for further development. We acknowledge that the type 1 error rate of 0.30 is liberal, and note that this was chosen based on the preliminary efficacy aspect of the study; post-analysis power calculations may be performed.

9.4 Analytic plan for secondary objectives

The mean, median and standard deviation of the change in the secondary endpoints other than CTCAE graded toxicities will be calculated in groups defined by randomized treatment assignment for all patients considered evaluable for the primary outcome measure. Analysis of secondary endpoints will be largely graphical and descriptive in nature. Between-group comparisons may consist of box-and-whisker plots, independent sample t-tests, or Mann-Whitney U-Test based on the distribution of the data.

9.5 Sample size justification

9.5.1 Pilot Portion

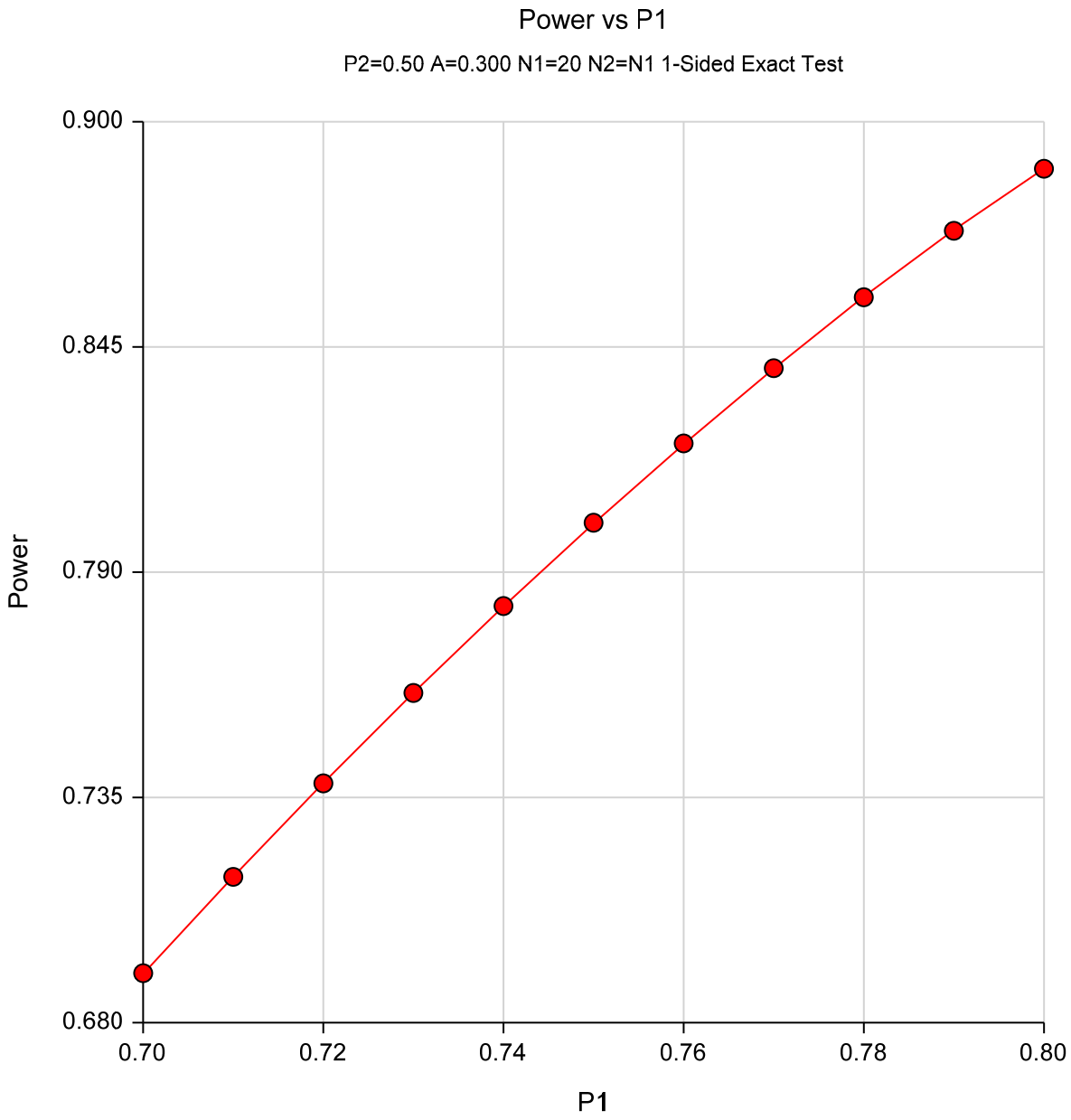
9.5.1.1 *For serious toxicities*: If the true rate of a "*serious toxicity*" with oral glyburide is 30%, the treatment will be considered not tolerable with probability 97%. If the regimen has a true rate of grade 3 hypoglycemia of 1%, the therapy will be considered tolerable with probability 90%.

9.5.1.2 *For concerning toxicities*: If the true rate of a "*concerning toxicity*" with oral glyburide is 30%, the treatment will be considered tolerable with probability 95%. If the regimen has a true rate of "*concerning toxicity*" of 70%, the therapy will be considered not tolerable with probability 85%.

9.5.1.3 The purpose of the pilot portion is to ensure feasibility of enrollment and safety of administering glyburide in patients with brain metastases that receive radiosurgery. These first 10 patients will undergo more extensive blood sugar evaluation than what is planned in the randomized portion. Once glyburide has been deemed safe and timely enrollment feasible, only then will we proceed to the randomized portion. The randomized portion will still assess hypoglycemia, but will utilize more standard hypoglycemia testing procedures. Our statistical group deemed 10 patients to be an appropriate number to ensure that rates of concerning hypoglycemia were not too high.

9.5.2 Randomized Portion: We expect the treatment success rate for the placebo will be 50% based on historical experience (15). The historical data from Hanna et al. was retrospectively evaluated from patients who received radiosurgery at University of Maryland. Many patients received dexamethasone during the course of radiosurgery and immediately thereafter, which likely resulted in a lower number of patients who experienced a clinical or radiographic increase in edema than if steroids were not utilized. The rationale for adding in a placebo group is to allow for a purer evaluation of the control

group, who will not be allowed to receive steroids unless they experience a clinical failure. As noted above, this selection design will use a type I error rate of 30%. A type I error rate of 30% is used because given the expected accrual in combination with limited funding available for the study, our goal is to determine if there is a signal for treatment success that would generate sufficient interest to escalate the study idea into a cooperative group setting, where the question of efficacy may be more definitively addressed. If the treatment success rate with glyburide is 75%, glyburide will be identified for further study with probability of 0.80. The power associated with other values for the treatment success probability for Glyburide is demonstrated in the figure below:



We project an inevaluability rate of at most 20%. The study will be completed with the enrollment of approximately 63 patients over an estimated 2 year enrollment period after approval.

10.0 REFERENCES

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APPENDIX I

"REGION GROWING" INSTRUCTIONS FOR ECLIPSE

1) After import MRI images into Eclipse, go to "**Contouring**", select the MRI image which you will use to contour, and double click. This should bring the selected image thumbnail to the top left portion of the screen.

Right Click on the image at the top left of the screen and select new structure. Under Label, type "Control Region". Under ID, type the name (example Edema_Pretx) and press "Create".

2) On the right taskbar, select "Imaging Threshold" and type in a range to encompass the hyperintense edema (Example Range 1000-2500). Click "Select VOI" and make the box encompass the area of edema at risk. Click Apply. If the range is not accurate, it may be modified.

3) This will create an ROI for edema that should then be modified by the physician to take out unnecessarily contoured structures (i.e. bone, calcifications, areas that are not consistent with edema. Edema should not include the appreciable gross tumor volume.

4) Select "Post Processing" and press "Apply to remove very small contoured areas.

5) Right click on the ROI at the top left and click "properties" to view and record the volume in cc's.

Separate ROIs maybe created for the gross tumor volume which should be manually contoured.

APPENDIX II

GLUCOSE MONITORING INSTRUCTIONS

HOW OFTEN SHOULD I CHECK MY BLOOD SUGAR?

4 Times a Day (the study team will let you know if you can check less often than 4 times a day):

1. Before breakfast (fasting)
2. Before lunch
3. Before dinner
4. At bedtime

More Often:

- When you feel symptoms of low or high sugars, illness, or stress
- When your doctor changes your medicine doses
- If you are more physically active than usual
- If you are pregnant or planning to become pregnant

Please write the results down in your blood glucose log and take it to all your clinic visits.

Why Should I Check My Blood Sugar?

Knowing what your blood sugar is:

- Helps you make decisions about how to eat, exercise, or take my medicine
- Lets you and us know if my any treatment needs to be changed

What Should my Blood Sugar be?

Before Meals: 80-130
2 Hours After Meals: Less than 180
Bedtime: 90-150

Less than 80 is too low.

If the patient is having symptoms that they think are related to their blood sugar level or if their blood sugar level is below 80, they will be instructed to check their fingerstick blood glucose level again and begin to try the items listed in "**Low Blood Sugar Interventions**", described in **Section 5.4.1.1** and **Appendix IV**. If "**Low Blood Sugar Interventions**" does not cause the blood sugar to rise above 80 after drinking or eating, or if their symptoms are not improving or worsening, the patient will be instructed to contact the study team and/or call 911 for emergency services.

APPENDIX III

HOW TO CHECK BLOOD GLUCOSE

MONITORING

How to Check Your Blood Glucose

(page 1 of 2 pages)

The only way to know how well your diabetes management plan is working is to check the amount of glucose that is in your blood throughout the day, every day.

Follow these steps when you check your blood glucose.

Step 1. Gather your supplies:

- home blood glucose meter
- testing strips
- **lancing device,** which makes it easier to stick your finger or forearm
- **lancet,** a tiny needle
- **sharps container,** a special plastic bottle in which you dispose of your lancets
- blood glucose record

Step 2. Wash and dry your hands, and the area you are lancing.

Step 3. Make sure you have enough blood in the area you are lancing.

For your finger, hang your hand at your side for a few seconds, or shake your hand several times. You can also squeeze the hand you are using with your other hand – in one motion from the palm of your hand to the fingertip. If you are lancing your forearm, rub it gently.

APPENDIX III – Continued…

HOW TO CHECK BLOOD GLUCOSE

MONITORING

How to Check Your Blood Glucose

(page 2 of 2 pages)

Step 4. Set up your meter.
Turn on your meter, if required. Most meters turn on when you insert a testing strip. Insert your testing strip as directed.

Step 5. Lance your finger or forearm.
Use your lancing device to get a drop of blood from your finger or forearm. The side of your finger hurts less than the finger tip. If you are lancing your arm, use the area closer to your elbow than your wrist.

Step 6.
Collect the blood on the testing strip.

Step 7. Read your results.

Step 8. Write the results in your blood glucose record.

There are many different meters available. Not every meter allows you to use your forearm. Use your meter as directed by the manufacturer. If you have questions or concerns, call the toll-free number found directly on the meter.

APPENDIX IV

HOW TO MANAGE LOW BLOOD SUGAR

Low Blood Sugar Interventions

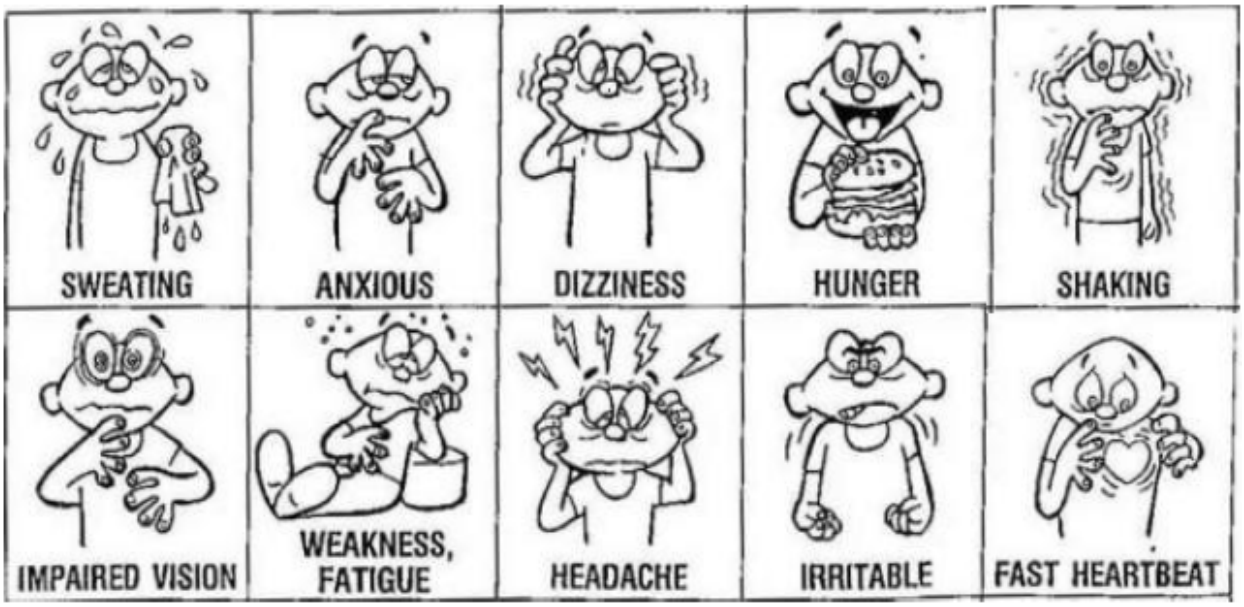
If you develop any of these symptoms during your time on study, please try:

- Drinking ½ cup of juice or soda
- Eating a few pieces of candy
- Taking 3 or 4 glucose tablets

If it will be more than an hour until meal time, try eating a snack that is high in starch. Snacks that are high in starch include:

- Crackers
- Bread
- Cookies

Symptoms include:



APPENDIX V

BLOOD GLUCOSE LOG

Day / Date		Breakfast		Lunch		Dinner		Bedtime	Comments
		Before	After	Before	After	Before	After		
Monday	Blood Glucose								
Date:	Time								
Tuesday	Blood Glucose								
Date:	Time								
Wednesday	Blood Glucose								
Date:	Time								
Thursday	Blood Glucose								
Date:	Time								
Friday	Blood Glucose								
Date:	Time								
Saturday	Blood Glucose								
Date:	Time								
Sunday	Blood Glucose								
Date:	Time								

APPENDIX VI

MEDICATION ADMINISTRATION LOG

In the appropriate area please indicate the time that you took your medication. Please remember to take your medication twice a day – in the morning with breakfast and in the evening with dinner. If you miss a dose, please do not make it up, just indicate it on this log by putting an X in the box where you missed your dose.

Please do not hesitate to call the research office if you have any questions or concerns.

Day	**Date**	**Time**	
		Morning Dose (AM)	Evening Dose (PM)
Monday			
Tuesday			
Wednesday			
Thursday			
Friday			
Saturday			
Sunday			
Monday			
Tuesday			
Wednesday			
Thursday			
Friday			
Saturday			
Sunday			
Monday			
Tuesday			
Wednesday			
Thursday			
Friday			
Saturday			
Sunday			

Signature: _____ Date: _____

APPENDIX VII

CTCAE version 4.0 and Toxicity Criteria

This study will utilize **NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for toxicity and Adverse Event Reporting**. A **grading** (severity) scale is provided for each Adverse Event (AE) term. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All investigators and study staff have access to a copy of the CTCAE version 4.0. Also, see Sections 5.3 and 7.3 for additional information.

An **Adverse Event (AE)** is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may *not* be considered related to the medical treatment or procedure.

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

- **Grade 1**: *Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.*
- **Grade 2**: *Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL).*
- **Grade 3**: *Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care Activities of Daily Living (ADL).*
- **Grade 4**: *Life-threatening consequences; urgent intervention indicated.*
- **Grade 5**: *Death related to AE.*

	GRADE				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Hypoglycemia	<LLN – 55mg/dL; <LLN – 3.0 mmol/L	<55-40 mg/dL; <3.0-2.2 mmol/L	<40-30 mg/dL; <2.2-1.7 mmol/L	<30 mg/dL; <1.7 mmol/L; life-threatening consequences; seizures	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of glucose in the blood.					

APPENDIX VIII
STUDY SCHEDULE OF EVENTS
PILOT PORTION

Assessments	Pretreatment		Treatment		Post Treatment		
	≤ 60 days prior to registration	≤ 14 days prior to registration	5-9 days prior to SRS	Day of SRS	7 days (1 wk) post SRS (± 3 days)	30 days (1 mo) post SRS (-5 to +10 days)	90 days (3 mo) post SRS (-10 to +14 days)
History and physical with neurological exam		C [1]				C	C
Documentation of steroid use		C	C	C	C	C	C
Glucose education / supply distribution [2]			R				
Fingerstick Glucose by patient			R [3]	R [3]	R [4]	R [5]	
Fingerstick Glucose by nurse/research team member			R		R	R	
Review of Medication and Glucose Logs					R	R	
CBC w/ diff and CMP including LFTs		C			C	C	C
Start Glyburide (should start at least 5 days prior to SRS)			R				
Stop Glyburide						R [5]	
Pregnancy test (if applicable)		C					
Contrast-enhanced MRI of the brain	C [6]					C [6]	C [6]
AE evaluation					C	C	C

C = Conventional Care. **R** = Research Related.

1. Baseline history and physical exam must include height and weight.
2. The patient will be supplied with a blood glucose monitor, a fingerstick glucose device, medication/blood glucose logs, and handouts for education purposes. The patient will be educated on how to measure and record blood glucose values. See Appendices II-VI.
3. Fingerstick glucose draws to be done by the patient 4 times a day (in the morning before breakfast (fasting), before lunch, before dinner, and before bed) beginning at least 5 days prior to SRS (the same day as starting glyburide) and continuing for at least 1 week after SRS.
4. Fingerstick glucose draws to be done by the patient once a day only if the patient doesn't have a concerning or serious toxicity at the 1 week post SRS visit. See Section 5.3.1 for further details.
5. The last dose of glyburide is taken on the evening of the day the 1 month post SRS MRI is done. Fingerstick glucose draws also discontinue at the same time as glyburide discontinuation.
6. MRI with and without contrast. T1-weighted, T2 and/or FLAIR MRI of the brain (maximum slice thickness 5mm). FLAIR imaging is preferred. Pretreatment MRI to be done within 21 days of SRS.

APPENDIX VIII *continued*
STUDY SCHEDULE OF EVENTS
RANDOMIZED PORTION

Assessments	Pretreatment		Treatment		Post Treatment		
	≤ 60 days prior to registration	≤ 14 days prior to registration	5-9 days prior to SRS	Day of SRS	7 days (1 wk) post SRS (± 3 days)	30 days (1 mo) post SRS (-5 to +10 days)	90 days (3 mo) post SRS (-10 to +14 days)
History and physical with neurological exam		C [1]				C	C
Documentation of steroid use		C	C	C	C	C	C
Glucose education / supply distribution [2]			R				
Fingerstick Glucose by patient			R [3]	R [3]	R [4]		
Fingerstick Glucose by nurse/research team member			R		R	R	
Review of Medication and Glucose Logs					R	R	
CBC w/ diff and CMP including LFTs		C			C	C	C
Start Investigational medication (should start at least 5 days prior to SRS)			R				
Stop Investigational medication						R [5]	
Pregnancy test (if applicable)		C					
Contrast-enhanced MRI of the brain	C [6]					C [6]	C [6]
AE evaluation					C	C	C

C = Conventional Care. **R** = Research Related.

1. Baseline history and physical exam must include height and weight.
2. The patient will be supplied with a blood glucose monitor, a fingerstick glucose device, medication/blood glucose logs, and handouts for education purposes. The patient will be educated on how to measure and record blood glucose values. See Appendices II-VI.
3. Fingerstick glucose draws to be done by the patient once a day beginning at least 5 days prior to SRS (the same day as starting investigational medication) and continuing for at least 1 week after SRS. See Section 5.4.2 for further details.
4. Fingerstick glucose draws to be done by the patient may be stopped only if the patient doesn't have a concerning or serious toxicity at the 1 week post SRS visit. See Section 5.3.2 for further details.
5. The last dose of the investigational medication is taken on the evening of the day the 1 month post SRS MRI is done.

6. MRI with and without contrast. T1-weighted, T2 and/or FLAIR MRI of the brain (maximum slice thickness 5 mm). FLAIR imaging is preferred. Pretreatment MRI to be done within 21 days of SRS.