Open Label Safety Study of Solriamfetol to Promote Wakefulness and Improve Cognition and Quality of Life in Patients with Primary Gliomas
Wake Forest Baptist Comprehensive Cancer Center
WFBCCC 98418
ClinicalTrials.gov: NCT03868943

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Participating Institution(s): WFBCCC

Version Date: 12-27-18
Amended: 05-19-21

Confidential

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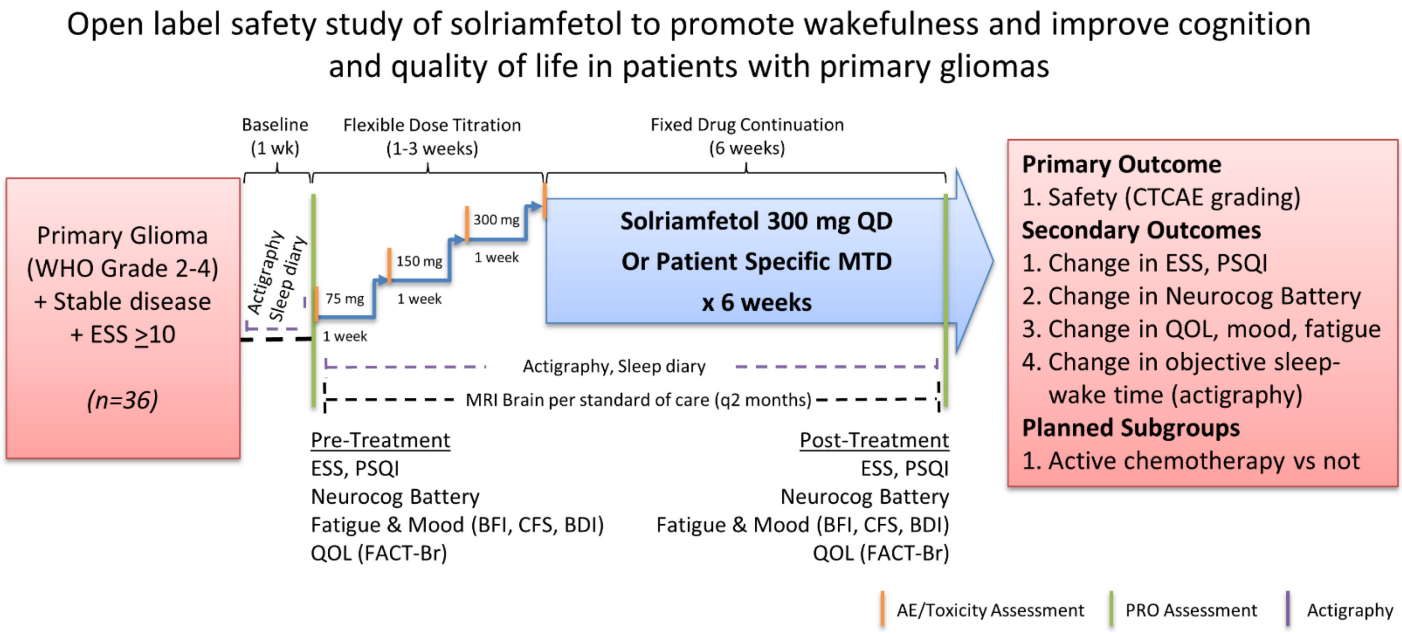

Open label safety study of solriamfetol to promote wakefulness and improve cognition and quality of life in patients with primary gliomas
Baseline (1 wk)
Flexible Dose Titration (1-3 weeks)
Fixed Drug Continuation (6 weeks)
Primary Glioma (WHO Grade 2-4) + Stable disease + ESS ≥10
(n=36)
Actigraphy
Sleep diary
75 mg
1 week
150 mg
1 week
300 mg
1 week
Solriamfetol 300 mg QD
Or Patient Specific MTD
x 6 weeks
Actigraphy, Sleep diary
MRI Brain per standard of care (q2 months)
Pre-Treatment
ESS, PSQI
Neurocog Battery
Fatigue & Mood (BFI, CFS, BDI)
QOL (FACT-Br)
Post-Treatment
ESS, PSQI
Neurocog Battery
Fatigue & Mood (BFI, CFS, BDI)
QOL (FACT-Br)
Primary Outcome
1. Safety (CTCAE grading)
Secondary Outcomes
1. Change in ESS, PSQI
2. Change in Neurocog Battery
3. Change in QOL, mood, fatigue
4. Change in objective sleep-wake time (actigraphy)
Planned Subgroups
1. Active chemotherapy vs not
AE/Toxicity Assessment
PRO Assessment
Actigraphy

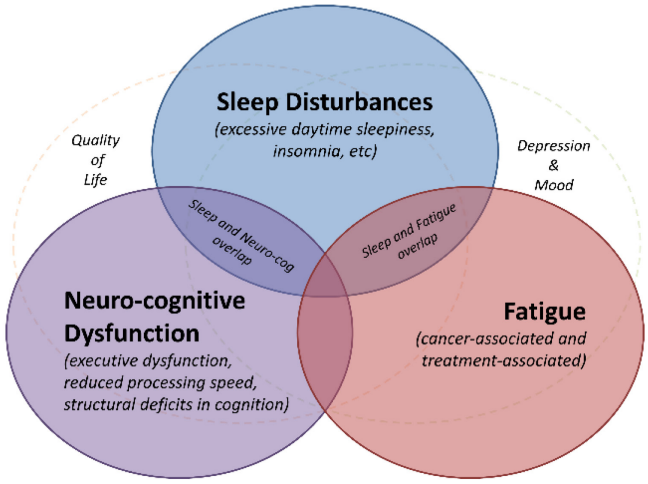
1 Background

Patients with primary brain tumors suffer from a unique constellation of symptoms that result from the tumor and its treatment, including (1) the infiltration of tumor into brain, (2) the effects of directing treatment toward the tumor (e.g. perioperative deficits, cerebral edema, radiation necrosis), and (3) short and long-term toxicities from treating the brain with radiation therapy (e.g. cognitive dysfunction, hormonal deficiences, etc), and chemotherapy (e.g. cognitive dysfunction, fatigue, etc). While the burden of symptoms is unique to each patient, several symptom clusters predominate including sleep-wake disturbances.

1. Sleep-wake Disturbance is Common in Brain Tumor Patients

Cancer-associated sleep-wake disturbances are common and reportedly affect up to 50-60% of cancer patients.[1–3] Sleep disruption occurs across the continuum of cancer care affecting 48% at the time of diagnosis,[4] 36% during cycle 1 of chemotherapy,[5] and 65% of cancer survivors.[6] The majority of prior studies have focused on breast and lung solid tumor patients, often excluding those with brain tumors.

Figure 1: Schematic Flow Diagram of the Sleep-Fatigue-Neurocognitive Symptom Cluster



A small number of studies have explored sleep disturbances in patients with primary brain tumors. A recent systematic review identified 11 primary research studies that evaluated sleep dysfunction in brain tumor patients. Many of these studies were retrospective reviews and often focused primarily on fatigue with sleep being a secondary or exploratory outcome. In these studies, sleep-wake disturbance was one of the 5 most common symptoms reported by brain tumor patients.[7] Sleep disturbances clustered with other symptoms including fatigue, depression, and cognitive impairment.[8] Such data support what clinicians have long appreciated in caring for these patients, that sleep-disturbances exist and co-occur with fatigue and neurocognitive dysfunction. This so-called sleep-fatigue-neurocognitive symptom cluster (Figure 1) results in significant quality of life impairment for patients, contributes to caregiver fatigue, and complicates the medical management of these patients for providers.

Sleep-disturbance is central to the symptom cluster displayed in Figure 1. Sleep disturbances are known to contribute to daytime fatigue and reduce daytime energy. Sleep-disturbances have been shown to contribute to poorer performance on neuro-cognitive batteries, reduce speed of processing, impair reflex times, and impair daily functioning.[7] As a result, interventions which target sleep dysfunction and address the symptoms observed within this cluster are extremely attractive and could substantially impact the lives of glioma patients.

2. Potential Causes of Sleep-wake Disturbance in Brain Tumor Patients

Primary brain tumor patients lie at a unique intersection between cancer-associated and neurological illness-related sleep disturbance where both the location of the tumor and its

oncologic treatment impact sleep-wake homeostasis. Cranial irradiation is one of the most significant factors associated with hypersomnia and sleep dysfunction.[9–11] However, numerous additional factors contribute to sleep disturbance including the frequent use of corticosteroids,[12] disruption of hypothalamic-pituitary axis signaling,[12] dysfunction in melatonin and hypocretin production,[13,14] timing of chemotherapy,[15–17] reduced physical activity due to neurological deficits,[18] anxiety and depression.[19–21]

Neuroinflammation may be a common mechanism underlying each of these clinical observations. Preclinical models indicate that elevated levels of circulating cytokines (e.g. IL-6, TGF-alpha, and IFN-gamma) contribute to alterations in norepinephrine, serotonin, dopamine, and melatonin signaling in brain tumor models.[22,23] These inflammatory mediators act on the brain via two pathways: (1) increased cytokine activity alters neurally-mediated signaling through the vagus nerve, and (2) activation of humoral immune pathways increase the expression of immune mediators (e.g. prostaglandins, COX-2, etc) at the blood-brain interface and promote a proinflammatory state in the central nervous system.[24–26] The link between sleep and neuroinflammation has gained particular attention recently. Studies aging, dementia, and Alzheimer's disease have suggested that poorer sleep may be associated with increased brain inflammation which if sustained chronically could contribute to an increased risk of subsequent dementia and neurocognitive deficits.[27–32]

In brain tumor patients, variations in melatonin production may be particularly important. Melatonin secretion functions as a regulator of the central molecular clock. Melatonin is synthesized in the pineal gland in response to inputs from the suprachiasmatic nucleus. Once synthesized, melatonin is released into both the cerebrospinal fluid and systemic circulation where it has pleiotropic actions on numerous organ-systems including the monoaminergic neurotransmitter system primarily through two receptor types, named MT1 and MT2.[33] As a result, melatonin serves as a key intermediary in the connection between sleep regulation and serotonin, dopamine, and norepinephrine signaling.[33] In fact, in addition to its actions on neurotransmitter signaling, melatonin has been shown to effect cerebral cytokine production, contribute to pro-inflammatory TNF-alpha secretion, and perpetuate the sleep-cognition-fatigue cluster in patients undergoing radiation therapy.[34–38]

These data support developing and testing pharmacologic agents with broad actions on neurotransmitter systems including the dopaminergic and noradrenergic systems to target the mechanistic drivers of sleep-disturbances in patients with primary brain tumors.

3. Prior Clinical Studies of Agents for Treating Sleep-Wake Disturbance in Gliomas

Prior intervention studies seeking to improve the sleep-fatigue symptom cluster in patients with primary brain tumors have not resulted in changes to clinical practice.

Modafinil was not better than placebo in improving patient symptoms. In fact 32% of patients dropped out of the study mostly due to treatment-related side effects.[8] In another study randomizing patients to either modafinil or methylphenidate, both agents were found to improve neuro-cognition but neither agent benefited patient reported increase in daytime sleepiness.[8] The majority of intervention studies have focused primarily on fatigue and neurocognitive outcomes (Table 1).[8,39–43] When included sleep has not been a primary outcome. Measures used to assess sleep dysfunction have varied and included the Epworth Sleepiness Scale (ESS), the brief sleep disturbance scale (BSDS), and in some studies, sleep has not been assessed at all. These data underscore the importance of exploring novel agents with new mechanisms that focus on sleep as the primary outcome.

Table 1: Clinical Studies of Agents for Treating Sleep-Fatigue-Neuro-cognition Symptom Cluster in Glioma Patients

Study / Author	Agent(s)	Primary Outcomes Measures	Key Study Finding
Gehring et al.[41]	Methylphenidate (2 doses) vs Modafinil	Cognitive function (cognitive battery), sleep (BSDS), mood, QOL (FACT-Br)	Similar improvements in cognition in both treatment arms, no change in sleep
Boele et al.[8]	Modafinil vs placebo	Fatigue (CIS), cognitive function (SF-Cog), mood (CES-D), QOL (SF-36)	No difference in fatigue, cognition, and mood between modafinil and placebo
Berk et al.[40]	Melatonin vs placebo	Survival	No difference in survival between melatonin and placebo
Lee et al.[42]	Armodafinil vs placebo	Radiation-induced fatigue (BFI, FACIT-F, CFS)	No difference in fatigue between armodafinil and placebo
Page et al.[43]	Armodafinil vs placebo	Radiation-induced fatigue (BFI, FACIT-F)	No difference in fatigue between armodafinil and placebo,

Caption: Quality of life, QOL. Brief fatigue inventory, BFI. Functional Assessment of Chronic Illness – Fatigue subscale, FACIT-F. Cancer-fatigue scale, CFS. Checklist individual strength, CIS. Center for epidemiologic studies depression scale, CES-D. Medical outcomes study short-form health survey, SF-36. Medical outcomes study short-form subjective cognitive functioning scale, SF-Cog. Brief sleep disturbance scale, BSDS. FACT-brain module, FACT-Br.

4. Preliminary Data on Sleep-Wake Disturbance in Gliomas and Rationale for Solriamfetol

At the American Academy of Neurology Annual Meeting, we recently presented the results of a pilot cross-sectional study evaluating the prevalence, risk factors, associated symptoms, and quality of life impact of self-reported sleep-wake disturbances in a cohort of patients with primary gliomas (Figure 2).

Figure 2: Study design from the prior cross-sectional study of sleep disorders in brain tumors patients

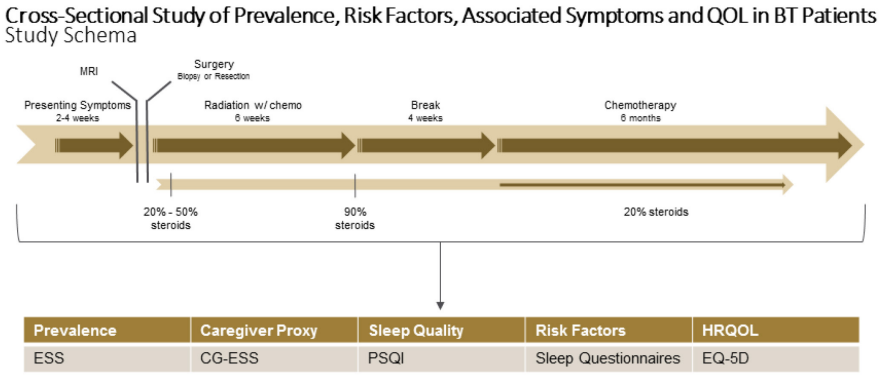
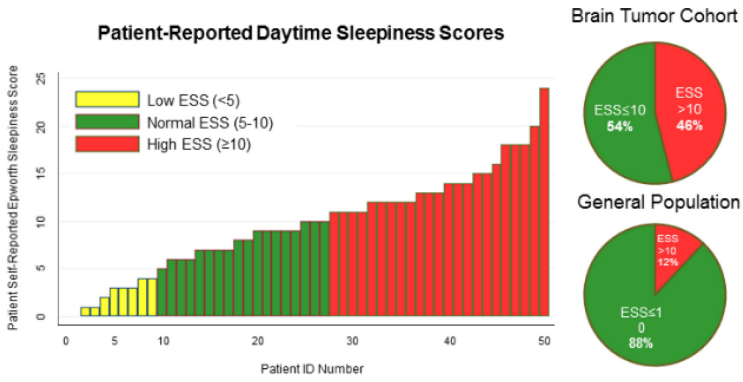


Figure 3: Prevalence of patient-reported excessive daytime sleepiness by Epworth Sleepiness Scale (ESS) scores



A prospective cohort of 50 brain tumor patients was recruited to complete a one-time survey-based assessment of self-reported sleep disturbance using the Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index (PSQI), a previously validated sleep hygiene and sleep habits questionnaire, as well as clinical and treatment characteristics, and quality of life (e.g. EQ-5D). In this study, excessive daytime sleepiness (EDS, ESS≥10) was reported in 46% of brain tumor patients (Figure 3). Patient-reported ESS was generally correlated with caregiver observed ESS for the patient (r=0.56, p=0.005), though important differences were present at the extremes of patient ESS. Abnormally low ESS (ESS<5) was observed in 16% of patients, meaning that a normal ESS score was only observed in 36% of the cohort. Self-reported excessive daytime sleepiness (ESS≥10) was significantly more common in patients who had ever undergone chemotherapy (42% vs 22%, p<0.008) but not radiation therapy (p=0.30) or by tumor grade (p=0.25). Fifty-two percent of patients on active corticosteroids had ESS≥10 compared to only 28% of those not taking corticosteroids (p=0.17). Chemotherapy treatment was associated with nighttime awakenings (p=0.04) while corticosteroid use was associated with lower daytime energy (p=0.04). EDS was also associated with poorer health-related QOL including reduced mobility (p<0.03) and impaired daily activities (p<0.02). These preliminary data support that:

1. Sleep-wake disturbances in the form of patient-reported excessive daytime sleepiness are common in brain tumor patients
2. That patient ESS can be used to evaluate self-reported sleep dysfunction given the correlation with caregiver observation, and
3. Indicate that a sufficient population can be identified by ESS≥10 for recruitment into an intervention study (roughly 50% of primary glioma patients)

5. Clinical Data on Solriamfetol for treating Excessive Daytime Sleepiness (EDS)

Solriamfetol (JZP-110) is a late stage investigational wakefulness-promoting agent that has been studied for the treatment of excessive daytime sleepiness (EDS). Prior studies have focused on adult patients with narcolepsy or obstructive sleep apnea. The mechanism of action of solriamfetol though not fully determined includes low potency dopamine and norepinephrine reuptake inhibition.[44] Solriamfetol's actions appear to be distinct from modafinil and traditional stimulants.

To date, solriamfetol has been found to be safe and well tolerated. Efficacy and safety have been demonstrated in several phase 2 and phase 3 studies. FDA approval is anticipated for treating EDS in patients with narcolepsy and obstructive sleep apnea.

1.5.1 Clinical Trials of Solriamfetol in Narcolepsy

To date, a Phase 2a, Phase 2b, and Phase 3 clinical trial has been conducted in patients with narcolepsy.[45–47]

Randomized Placebo-Controlled Phase 2a Trial in Narcolepsy[47]
The Phase 2a trial was a 4-week, double-blind, placebo-controlled, multicenter, randomized, cross-over study. Participants were between the ages of 18 and 65 years in good general health with documented EDS due to narcolepsy as per the International Classification of Sleep Disorders, Second Edition (ICSD-2) criteria. Patients who had a baseline Epworth Sleepiness Scale (ESS) score greater than or equal to 10 and a baseline mean sleep latency on the Maintenance of Wakefulness Test (MWT) of less than or equal to 10 minutes were included. Exclusion criteria included customary bedtime later than midnight; history of significant medical condition, behavioral or psychiatric disorder (including suicidal ideation), or surgical history; any other clinically relevant medical, behavioral or psychiatric disorder other than narcolepsy associated with daytime sleepiness, body mass index (BMI) greater than 34; excessive caffeine use (>600 mg/day or >6 cups of coffee/day); nicotine dependence that had an effect on sleep; and history of alcohol or drug abuse within the past 2 years. Patients were randomized to one of two treatment sequences: either placebo administration for 2 weeks followed by solriamfetol for 2 weeks, or the reverse sequence. Dosing was begun at 150 mg/day for 1 week and increased to 300 mg/day for the second week. The primary efficacy endpoint was the change from baseline in average sleep latency time across the 4 MWT trials performed 2 hours apart at the end of 2 weeks of treatment. Secondary endpoints included the change from baseline in ESS scores and Clinical Global Impression-Change (CGI-scores) at the end of 1 and 2 weeks of treatment.

Thirty-three patients were randomized and completed both the placebo and solriamfetol periods. The change from baseline in average sleep latency from 4 MWT trials (primary endpoint) was 12.7 minutes for solriamfetol and 0.9 minutes for placebo, a statistically significant difference of 11.8 minutes (p=0.0002). Additionally, the sleep latency on each of the 4 individual MWT trials was statistically significantly longer for solriamfetol than for placebo (9 to 14.6 minutes longer; p<0.001). On the ESS scores, there was a mean change of -5.3 for solriamfetol compared to -1.2 for placebo (p<0.0001) following 1 week of treatment (150 mg/day); and a mean change of -6.7 for solriamfetol compared to -2.4 for placebo (p=0.0002) following 2 weeks of treatment (300 mg/day during the second week). The CGI-C ratings demonstrated that 88% of patients on solriamfetol showed improvement at 1 week of treatment compared to 27% of patients on placebo (p<0.0001); and at 2 weeks of treatment 76% of patients on solriamfetol and 39% of patients on placebo showed improvement (p=0.0016).

Adverse events occurring with ≥5% incidence with solriamfetol (150 mg/day and 300 mg/day combined) included nausea (n=4; 12%), headache (n=3; 9%), non-cardiac chest discomfort (n=3; 9%), anxiety (n=2; 6%), decreased appetite (n=2; 6%), initial insomnia (n=2; 6%), insomnia (n=2; 6%), and muscle tightness (n=2; 6%). Fourteen patients (42%) experienced 1 or more adverse event(s) with solriamfetol (combined 150 mg/day and 300 mg/day).

Randomized Placebo-Controlled Phase 2b Trial in Narcolepsy[46]
The Phase 2b trial was a 12-week, double-blind, placebo-controlled, multicenter, parallel design study. Patients were randomized to receive either placebo (once daily) or solriamfetol (150 mg/day during Weeks 1 through 4 and 300 mg/day during Weeks 5 through 12). The co-primary endpoints were the change from baseline to last assessment in average sleep latency time as determined by the MWT and the change from baseline to last assessment on the CGI-C. Change in disease status from baseline was assessed at 1, 2, 4, 6, 8, and 12 weeks using the

CGI-C and the Patient Global Impression of Change (PGI-C) scales. Secondary endpoints included the change from baseline in ESS score at Week 4 and Week 12.

Ninety-three patients were randomized in the study, of whom 49 patients were randomized to placebo and 44 patients to solriamfetol. The 2 treatment groups were similar in demographic and clinical characteristics. The sample was 64.5% female, 74.2% white with a mean (standard deviation [SD]) age of 38.7 (12.1) years and a baseline mean (SD) ESS score of 17.3 (3.3). At Week 4, there were statistically significant differences in the change from baseline with solriamfetol relative to placebo in average sleep latency on the MWT (increase of 9.5 minutes for solriamfetol vs. 1.4 minutes for placebo; p<0.0001); CGI-C ratings (80% improved for solriamfetol vs. 51% improved for placebo; p=0.0066); and ESS scores (decrease of 5.6 points for solriamfetol vs. 2.4 points for placebo; p=0.0038). At Week 12, treatment with solriamfetol resulted in statistically significantly greater changes from baseline compared with placebo in average sleep latency on MWT (12.8 minutes for solriamfetol vs. 2.1 minutes for placebo; p<0.0001); ESS scores (8.5 points for solriamfetol vs. 2.5 points for placebo; p<0.0001); and proportion of patients with improvement on the CGI-C (86% for solriamfetol vs. 38% for placebo; p<0.0001). Also at Week 12, statistically significantly more patients improved on the PGI-C with solriamfetol compared with placebo (93.0% for solriamfetol vs. 38.3% for placebo; p<0.0001). The percentage of PGI-C scores that matched the CGI-C scores was 74.4%, with a strong and significant correlation between the scores (Spearman r = 0.868; p<0.0001). The 10 patients who reported they were “very much improved” on the PGI-C at Week 12 had a mean reduction of 76.7% on the ESS, and the 33 patients who reported they were “much improved” on the PGI-C at Week 12 had a mean decrease in ESS score of 49.1%. Three patients (6.8%) randomized to solriamfetol discontinued due to adverse events. The most common adverse events occurring in patients in the solriamfetol and placebo groups, respectively, were headache (16%, 10%), nausea (14%, 6%), diarrhea (11%, 6%), insomnia (14%, 2%), decreased appetite (14%, 0%), and anxiety (11%, 0%). Two serious adverse events (conversion disorder and acute cholecystitis) occurred in the solriamfetol group; these adverse events were considered probably unrelated to the study drug by the investigators.

Randomized Placebo-Controlled Phase 3 Study in Narcolepsy[45]
The Phase 3 study was a 12-week, double-blind, randomized, placebo-controlled, parallel group study evaluating the safety and efficacy of solriamfetol for the treatment of excessive sleepiness and impaired wakefulness in patients with narcolepsy. Patients were randomized 1:1:1:1 to receive daily placebo or solriamfetol 75 mg, 150 mg, or 300 mg, and randomization was stratified by the presence or absence of cataplexy. The co-primary study endpoints were the change from baseline to Week 12 in mean sleep latency on the MWT and the change from baseline to Week 12 in the ESS score. The key secondary endpoint was the percentage of patients who reported improvement on the Patient Global Impression of Change (PGI-C) at week 12. Evaluation of safety included adverse events (AEs), laboratory tests, and vital signs.

Of the 239 patients randomized, 236 received at least one dose of study drug and were included in the safety population.[2] The modified intention to treat (mITT) population consisted of 231 patients, of whom 58 patients were randomized to placebo, 59 patients to solriamfetol 75 mg, 55 patients to solriamfetol 150 mg, and 59 patients to solriamfetol 300 mg. A total of 195 patients completed the study (52 patients in the placebo group, 49 in the solriamfetol 75 mg group, 51 in the solriamfetol 150 mg group, and 43 in the solriamfetol 300 mg group). In the mITT population (n=231), the discontinuation rate was highest in the solriamfetol 300 mg group (27.1%) compared with the placebo (10.3%), solriamfetol 75 mg (16.9%), and solriamfetol 150 mg (7.3%) groups. The most common reasons for discontinuation in the solriamfetol 300 mg group were lack of efficacy (10.2%, n=6) and adverse events (8.5%, n=5).

Demographics and clinical characteristics were similar among treatment groups at baseline, and participants were mostly white, female, age in the mid-thirties, and with a BMI over 25 kg/m^2. Patients had excessive sleepiness at baseline as indicated by ESS scores and MWT mean sleep latency times. The study met the co-primary endpoints of change from baseline in MWT and ESS and the key secondary endpoint of percentage of patients with improvement on PGI-C at solriamfetol-150 mg and 300 mg at week 12 (Table 2). Statistical significance was not achieved for solriamfetol 75 mg on the MWT.

Table 2. Hierarchical Testing of Co-Primary and Key Secondary Efficacy Endpoints in the Modified Intent-to-Treat Population (Week 12)

Endpoint	Solriamfetol 300 mg	Solriamfetol 150 mg	Solriamfetol 75 mg
Maintenance of Wakefulness Test	<0.0001	<0.0001	0.1595
Epworth Sleepiness Scale	<0.0001	<0.0001	0.0211
Patient Global Impression of Change	<0.0001	<0.0001	0.0023*

Table displays p-values.
*Nominal p-value since below the hierarchical break.

Solriamfetol 150 mg and Solriamfetol 300 mg significantly increased MWT mean sleep latency relative to placebo at week 12 in the mITT population. Statistically significant effects were seen as early as week 1 for Solriamfetol 150 mg and 300 mg, and continued throughout the 12 weeks of the study. The effects on the MWT appeared to be dose-dependent over the 12 weeks of the study. At Week 12, Solriamfetol at all doses significantly reduced ESS scores from baseline relative to placebo in the mITT population (Table 3). Statistically significant effects were observed for Solriamfetol 150 mg and 300 mg as early as week 1. Effects on the ESS were dose-dependent over the 12 weeks of the study.

Table 3. Mean Change from Baseline on the Epworth Sleepiness Scale Score

Group	Least Squares Mean Change from Baseline on ESS Score			
	Week 1	Week 4	Week 8	Week 12
Placebo (n=58)	–2.7	–2.2	–2.1	–1.6
Solriamfetol 75 mg (n=59)	–3.2	–3.3	–3.4	–3.8†
Solriamfetol 150 mg (n=55)	–5.5†	–5.6*	–5.2†	–5.4*
Solriamfetol 300 mg (n=59)	–6.7*	–5.6*	–6.4*	–6.4*

†p<0.05 vs. placebo.
*p<0.0001 vs. placebo

The most common (≥5%) adverse events (AEs) in all solriamfetol groups were headache, nausea, decreased appetite, nasopharyngitis, dry mouth, and anxiety. In general, the incidence of the most common AEs was dose-dependent. One patient in the solriamfetol 150 mg group had 2 serious AEs consisting of non-cardiac chest pain and anxiety that were deemed not to be related to the study drug by the investigator. This patient continued in the study. Discontinuations due to AEs were greater in the solriamfetol 150 mg and 300 mg groups than in the placebo group.

1.5.2 Clinical Trials in Obstructive Sleep Apnea

Solriamfetol has also been studied in clinical trials in patients with EDS from obstructive sleep apnea (OSA).[48]

Randomized, Placebo-Controlled, Double-Blind, 12-Week Multicenter Study in OSA

A 12-week, double-blind, randomized, placebo-controlled parallel design study evaluated the efficacy and safety of solriamfetol for the treatment of excessive sleepiness in adult patients with OSA. Patients were randomized in a 1:1:2:2:2 ratio to solriamfetol 37.5 mg, 75 mg, 150 mg, 300 mg, or placebo and stratified by adherence to OSA treatment. The co-primary efficacy endpoints were the change from baseline to week 12 on the MWT and the ESS. The study was completed by a total of 404 patients (101, 49, 54, 106, and 94 patients in the placebo, solriamfetol 37.5 mg, solriamfetol 75 mg, solriamfetol 150 mg, and solriamfetol 300 mg groups, respectively). The overall number of discontinuations was highest in the solriamfetol 300 mg group (n=21) relative to the numbers of patients discontinued in the placebo group (n=13), solriamfetol 37.5 mg group (n=7), solriamfetol 75 mg group (n=4), and solriamfetol 150 mg group (n=10). The baseline characteristics were similar among the treatment groups. All doses of solriamfetol met the co-primary endpoints. Effects were dose-dependent and the greatest effect was seen at the solriamfetol 150 mg and 300 mg doses.

Solriamfetol at all doses significantly increased the mean MWT sleep latency at weeks 4 and 12, and at the 75 mg, 150 mg, and 300 mg doses as early as week 1. At the 150 mg and 300 mg doses, solriamfetol increased the mean MWT sleep latency by over 10 minutes at all time points. Increases in mean MWT sleep latency were dose-dependent across the duration of the study solriamfetol significantly decreased ESS scores at all doses at week 12 and as early as week 1 (Table 4). Decreases in ESS score were dose-dependent across the study duration. At week 12, solriamfetol at the 150 mg and 300 mg doses decreased mean ESS scores by more than 7 points.

Table 4. Mean Change from Baseline on the Epworth Sleepiness Scale (ESS) Score at Weeks 1, 4, 8, and 12

Group	Least Squares Mean Change from Baseline on the Epworth Sleepiness Scale Score			
	Week 1	Week 4	Week 8	Week 12
Placebo (n=114)	–2.6	–2.9	–3.8	–3.3
Solriamfetol 37.5 mg (n=56)	–4.5†	–4.7†	–4.7	–5.1†
Solriamfetol 75 mg (n=58)	–4.4†	–4.8†	–6.3†	–5.0†
Solriamfetol 150 mg (n=116)	–5.5*	–6.1*	–6.9*	–7.7*
Solriamfetol 300 mg (n=115)	–6.6*	–6.6*	–7.7*	–7.9*

†p<0.05 vs. placebo.
*p<0.0001 vs. placebo

The most common AEs (≥5%) across all doses of solriamfetol were headache, nausea, decreased appetite, anxiety, and nasopharyngitis. Seven serious AEs were reported in 5 patients, which consisted of goiter (n=1) and motor vehicle accident, back pain, and sciatica (n=1) in the placebo group; bile duct obstruction (n=1) and streptococcal endocarditis (n=1) in the solriamfetol 37.5 mg group, and hyperglycemia (n=1) in the solriamfetol 150 mg group. There was one non-treatment related serious adverse event of coronary artery disease that began prior to the patient receiving solriamfetol 300 mg. Solriamfetol had a modest effect on blood pressure and pulse rate, with a mean increase from baseline of 1 to 4 mm Hg in systolic blood pressure and 1 to 3 mm Hg in diastolic blood pressure, and a mean increase from baseline of 2 to 5 beats per minute in pulse rate.

Placebo-Controlled, Randomized-Withdrawal, Double-Blind, 6-Week Study in OSA
A double-blind, placebo-controlled, randomized-withdrawal designed study evaluated the safety and efficacy of solriamfetol administered once daily compared with placebo for the treatment of excessive sleepiness in adults with OSA. The study included adult patients aged 18 to 75 years with OSA diagnosed according to ICSD-3 criteria, along with current or prior use of a primary OSA therapy including CPAP, oral appliances, or surgical intervention, a baseline ESS score of 10 or greater, a baseline MWT mean sleep latency of less than 30 minutes on the first 4 trials of a 5-trial, 40-minute MWT, and a usual nightly sleep time of 6 hours or more. The study began with a Screening Phase lasting up to 28 days, which was followed from baseline to week 2 by a Titration Phase. During the Titration Phase, patients started on a once daily dose of solriamfetol 75 mg and could be titrated up or down every 3 days up to a maximum tolerated dose of solriamfetol 75 mg, 150 mg, or 300 mg. A 2-week Stable Dose Phase (week 2 to week 4) followed, and during this phase patients continued to receive the dose they were titrated to in the Titration Phase for 2 weeks. During the following Double-Blind Withdrawal Phase (week 4 to week 6), patients who reported “much” or “very much” improvement on the PGI-C scale, and who had improved on the MWT and ESS at week 4 were randomized in a 1:1 ratio based on

primary OSA therapy compliance to receive the same current dose of solriamfetol or placebo for 2 weeks. A Safety Follow-Up period took place for 2 weeks from week 6 to week 8.
The co-primary efficacy endpoints were the change from week 4 to 6 on the MWT and the ESS. A key secondary endpoint was the percentage of patients reported as worse on the PGI-C and CGI-C, in which they were assessed on a 7-point scale from 1 (very much improved) to 7 (very much worse). Of the 402 patients who were screened, 174 patients were enrolled in the Titration Phase and received at least 1 dose of solriamfetol, and were included in the safety population. Seventeen of the 174 patients (10%) discontinued in the Titration Phase, 9 of 157 patients (6%) discontinued in the Stable-Dose Phase, and an additional 21 patients (14%) did not meet the improvement criteria for randomization. In the Stable-Dose Phase there were 14.6%, 31.8%, and 53.5% of patients in the solriamfetol 75, 150, and 300 mg groups, respectively. The safety population that was randomized to double-blind withdrawal included 62 patients randomized to solriamfetol and 62 patients randomized to placebo. In the Double-Blind Withdrawal Phase there were 7.3%, 21.0%, and 21.8% of patients in the solriamfetol 75 mg, 150 mg, and 300 mg groups, respectively. Two patients discontinued in the Double-Blind Phase; thus, the mITT population consisted of 122 patients (placebo [n=62] and solriamfetol [n=60]).

Baseline values for the MWT and ESS in the mITT population were similar for those in the safety population. After 4 weeks of solriamfetol treatment, MWT sleep latencies increased from approximately 12-13 minutes to approximately 30 minutes and ESS scores decreased from approximately 15-16 to approximately 6 in the mITT population. During the Double-Blind Withdrawal Phase (from week 4 to week 6), patients who had improved on solriamfetol, and who continued to receive solriamfetol, remained improved on the MWT and ESS, whereas patients who were switched to placebo worsened on both measures. From week 4 to week 6 (Double-Blind Withdrawal Period), the mean MWT sleep latency went from 31.7 minutes to 29.7 minutes and the mean ESS score remained at 6.4 at both time points in the solriamfetol group (n=60), while in the placebo group (n=62) the mean MWT sleep latency values went from 29.0 minutes to 17.6 minutes and the mean ESS score went from 5.9 to 10.8.

The mean MWT sleep latency decreased by 12.1 minutes from week 4 to week 6 in patients who were switched to placebo during the Double-Blind Withdrawal Phase compared with a change of -1.0 minute for those who remained on solriamfetol ($p<0.0001$). Mean ESS scores increased by 4.5 among patients who were switched to placebo during the Double-Blind Withdrawal Phase, compared with a mean decrease of 0.1 for those who stayed on solriamfetol ($p<0.0001$).

More AEs occurred during the Titration Phase (48.9%) than during the Stable Dose Phase (10.2%). The most common AEs (≥5%) during the Titration Phase were headache, dry mouth, nausea, dizziness, and insomnia.

6. Summary of Study Rationale

In summary, sleep dysfunction is common in brain tumor patients and clusters with fatigue, neurocognitive dysfunction, and poor quality of life. Widespread alterations in neurotransmitters and cytokine signaling suggest a need to intervene with an agent that targets neurotransmitter signaling as opposed to daytime stimulants (e.g. methylphenidate) or circadian agents (e.g. melatonin). The combined dopaminergic and noradrenergic activity of solriamfetol set it apart from other agents (e.g. modafinil) that have been previously tested and have shown signals of activity on this symptom cluster. Existing therapeutic studies caution against early efficacy studies until safety is determined given the potential for antiepileptic drug and corticosteroid drug-drug interactions, sensitivity of these patients to psychoactive agents, risk of increasing seizure activity, and the susceptibility of this population to drug-induced cognitive dysfunction.

Solriamfetol is an ideal agent for testing. The drug's combined norepinephrine and dopamine reuptake inhibitor properties are attractive in glioma patients who have widespread neurotransmitter dysfunction and a symptom cluster that includes impairments in fatigue, mood, and neuro-cognition.[40,44]

Safety is an important first step and study outcome. In the published phase 2 and 3 studies of solriamfetol in patients with narcolepsy or obstructive sleep apnea (OSA), adverse events included headache (9-16%), nausea (12-14%), diarrhea (11%), decreased appetite (6-14%), anxiety (6-11%), chest discomfort (9%), insomnia (6%), muscle tightness (6%), nasopharyngitis (5-14%), and dry mouth (5-10%). Cancer patients and in particular brain tumor patients are at risk for some of these and other cognitive, seizure, or neurological toxicities that need to be explored at each of solriamfetol's three dose levels (75 mg, 150 mg, 300 mg) prior to proceeding to a primary efficacy endpoint. The current trial will establish this experience.

Prior studies of solriamfetol have shown early improvements in patient-reported sleep by ESS scores. In the current study we will also evaluate other associated symptoms of fatigue, neurocognition, mood, and quality of life. It is not clear that these associated symptoms will respond as quickly to drug therapy. In fact, according to our model of the sleep-fatigue-neurocognitive symptom cluster (Figure 1), we suspect that improvement in fatigue, neurocognition, mood and quality of life are downstream of the improvement in sleep and thus, in this study, endpoints will be assessed after prolonged stable drug therapy. This should not affect the ability to assess for improvements in sleep which have been reported as early as 1 week after solriamfetol treatment and remained stable over up to 12 weeks of continued treatment in the aforementioned studies.

2 Hypotheses

1. Primary Hypothesis

We hypothesize that the side effect profile of solriamfetol at doses of 75 mg daily, 150 mg daily, and 300 mg daily will be similar in patients with primary brain tumors to that reported in patients with narcolepsy and obstructive sleep apnea.

Serious adverse events in patients with primary brain tumors including significant confusion/altered mental status, seizures, or other side effects will not be more common at the 300 mg daily dose compared to the 150 mg and 75 mg daily doses.

2. Secondary Hypotheses

Secondary hypotheses include that solriamfetol treatment at maximal patient specific dosing will result in improvements in patient-reported excessive daytime sleepiness and sleep quality (e.g. ESS and PSQI), neurocognitive function (see below for neurocognitive battery), fatigue and mood (e.g. Brief Fatigue Inventory, Cancer Fatigue Scale, Beck Depression Inventory), and quality of life (FACT-Brain).

3. Exploratory Hypotheses

Improvements in objective measures of sleep (e.g. actigraphy, sleep diary) will be similar to those reported in prior studies (e.g. obstructive sleep apnea, narcolepsy). We hypothesize that improvements in sleep, neurocognition, fatigue, mood, and quality of life may vary by clinical factors such as corticosteroid use, antiepileptic use, and tumor grade by World Health Organization (WHO) classification.

3 Objectives

1. Primary Objective(s)

1. To estimate the safety of solriamfetol at 75 mg daily, 150 mg daily, 300 mg daily as assessed by NCI CTC Adverse Events (v5.0) in patients with primary gliomas compared to prior studies[45–47]

2. Secondary Objective(s)

1. To estimate the effect of solriamfetol on sleep by Epworth Sleepiness Scores (ESS) scores in patients with primary gliomas and compare the effect to previously published scores in patients with OSA

2. To estimate the effect of solriamfetol on sleep quality by Pittsburgh Sleep Quality Index scores

3. To estimate the effect of solriamfetol on neurocognitive function based on a disease-specific neurocognitive battery (see neurocognitive battery below)

4. To estimate the effect of solriamfetol on patient-reported fatigue (Brief Fatigue Inventory, Cancer Fatigue Scale) & mood (Beck's Depression Inventory)

5. To estimate the effect of solriamfetol on patient-reported QOL (FACT-Br)

6. To estimate the effect of solriamfetol on objective sleep-wake times by actigraphy and sleep diary (pre- vs post-treatment)

3. Exploratory Objective(s)

1. To explore a biologic gradient effect of increasing doses of solriamfetol on actigraphy

2. To explore differences in clinical activity of solriamfetol by corticosteroid use, antiepileptic use, and tumor grade

4 Patient Selection

Inclusion and exclusion criteria represent standard criteria for other sleep studies in this population (e.g. inclusion criteria) and standard exclusions for prior studies of this agent (e.g. exclusion criteria).[8,39,40]

1. Inclusion Criteria

1. WHO Grade 2-4 infiltrating glioma by histologic confirmation

    - Where appropriate results from clinically available testing of isocitrate dehydrogenase (IDH) gene mutation status (for all gliomas), chromosome 1p and 19q deletion status (for suspected oligodendrogliomas), and MGMT gene promoter methylation status (for malignant gliomas) must be available in the patient's chart.

- These studies are standard of care molecular studies that are performed as a part of routine clinical practice and allow for integrated molecular subtyping of primary glial tumors.

2. Epworth Sleepiness Scale (ESS) score ≥10 within 21 days of enrollment

3. Clinical and/or radiographic evidence of stable disease within 21 days of enrollment

4. Patients must have completed ***concurrent*** chemoradiation with recovery of all pre-existing toxicity to CTCAE Grade >1

    - Patient who are anticipated to undergo surgery and/or radiation therapy for management of their tumor during the duration of study treatment are NOT eligible.

    - Patients who are anticipated to undergo adjuvant chemotherapy are eligible as long as there is no evidence of tumor progression by clinical exam and/or imaging within 21 days of enrollment (see 4.1.2). This determination should be made by clinical documentation and if there is question discussed with the Study Chair. Adjuvant chemotherapy is not an exclusion.

    - Patients who are currently undergoing chemotherapy, targeted therapy, immunotherapy, or salvage treatment and have stable disease by imaging are eligible and can continue the current anti-cancer therapy. Patients who will require a new anti-cancer treatment or are anticipated to change anti-cancer treatments are not eligible.

5. Age ≥ 18 years

6. Karnofsky performance status ≥ 60%

7. Life expectancy of greater than 4 months

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

-	leukocytes	≥3,000/mcL
-	absolute neutrophil count	≥1,500/mcL
-	platelets	≥100,000/mcL
-	total bilirubin	1.5 X institutional upper limits of normal
-	AST(SGOT)/ALT(SGPT)	≤2.5 X institutional upper limit of normal
-	creatinine	within normal institutional limits
	OR	
-	creatinine clearance	≥50 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.

9. The effects of solriamfetol on the developing human fetus are unknown. For this reason women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is

pregnant while participating in this study, she should inform her treating physician immediately

10. Ability to understand and the willingness to sign an IRB-approved informed consent document (either directly or via a legally authorized representative)

2. Exclusion Criteria

1. Receiving active radiation therapy (including patients who are within 28 days of completing radiation therapy)

2. Anticipated to undergo radiation therapy or require neurosurgical intervention during the period of active treatment (i.e. within the next 4 months)

3. Contraindication to solriamfetol based on drug-drug interactions or concurrent systemic illness that precludes drug treatment

4. Patients who have not recovered to <CTCAE grade 2 toxicities related to prior or current therapy are ineligible.

    - Exception for laboratory-based or other adverse event that is stable and not anticipated to interfere with study related treatment must be reviewed and approved by the Study Chair.

5. Customary bedtime later than midnight

6. Known and/or documented history of obstructive sleep apnea (OSA)
7. Uncontrolled behavioral or psychiatric disorder (including suicidal ideation)

8. Current excessive caffeine use (>600 mg/day or >6 cups of coffee/day)

9. Current or prior history of alcohol or drug abuse within the last 2 years as assessed by the treating clinician

10. Nicotine dependence that is currently interfering with sleep based on assessment by the treating clinician

11. Concurrent use of selective serotonin or norepinephrine reuptake inhibitors (e.g. SSRI, SNRI) within 14 days of study enrollment

    - Patients who are currently taking these agents may be tapered at the direction of the treating physician prior to study enrollment.

    - Patients taking other medications such as narcotics, benzodiazepines, antipsychotics, antiepileptics, corticosteroids, or over-the-counter sleep aids can be enrolled. It is recommended that the doses of these medications remain the same throughout the portion of active study treatment unless there is a medical indication for dose adjustment which will be determined by the treating physician (see Section 7.10).

12. History of allergic reactions attributed to compounds of similar chemical or biologic composition to solriamfetol

13. Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements

14. Pregnant women are excluded from this study because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with – solriamfetol, breastfeeding should be discontinued if the mother is treated with solriamfetol

3. Inclusion of Women and Minorities

Men and women of all races and ethnicities who meet the above-described eligibility criteria are eligible to participate in this study.

5 Registration Procedures

All patients entered on any WFBCCC trial, whether treatment, companion, or cancer control trial, **must** be linked to the study in EPIC within 24 hours of Informed Consent. Patients **must** be registered prior to the initiation of treatment.
You must perform the following steps in order to ensure prompt registration of your patient:

1. Complete the Eligibility Checklist (Appendix A)
2. Complete the Protocol Registration Form (Appendix B)
3. Alert the Cancer Center registrar by phone, *and then* send the signed Informed Consent Form, Eligibility Checklist and Protocol Registration Form to the registrar, either by fax or e-mail.

   Contact Information:
   Protocol Registrar PHONE [redacted]
   Protocol Registrar FAX [redacted]
   Protocol Registrar E-MAIL [redacted]

   *Protocol Registration is open from 8:30 AM - 4:00 PM, Monday-Friday.

4. Fax/e-mail ALL eligibility source documents with registration. Patients **will not** be registered without all required supporting documents.

Note: If labs were performed at an outside institution, provide a printout of the results. Ensure that the most recent lab values are sent.

To complete the registration process, the Registrar will:

- assign a patient study number
- register the patient on the study

6 Study Outcomes and Study Measures

This is a single-arm, open label, non-randomized safety study in patients with glioma with each patient undergoing both a dose-escalation and fixed drug continuation phase of the study. The primary objective is to compare the safety of oral solriamfetol at doses of 75 mg daily, 150 mg daily and 300 mg daily. Secondary objectives include determining the effect of solriamfetol on patient-reported sleep, neurocognition, fatigue, mood, quality of life, and objective measures of sleep.

1. Primary Outcome

1. The primary outcome measure will be adverse events as assessed by the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

2. Secondary Outcomes

1. The effect of solriamfetol on patient-reported sleep will be assessed by Epworth Sleepiness Scale (ESS) scores

2. The effect of solriamfetol on patient-reported sleep quality will be assessed by Pittsburgh Sleep Quality Index (PSQI) scores.

3. The effect of solriamfetol on neurocognitive function will be assessed by a disease-specific Neurocognitive Battery (Section 7.8).

4. The effect of solriamfetol on patient-reported associated symptoms will be assessed by the Brief Fatigue Inventory (BFI) and the Cancer Fatigue Scale (CFS) for determining the effect on fatigue and by the Beck's Depression Inventory (BDI) for determining the effect on depression and mood.

5. The effect of solriamfetol on patient-reported QOL will be assessed by the FACT-Brain module (FACT-Br).

6. The effect of solriamfetol on changes in objective sleep-wake times will be assessed by actigraphy and patient-reported sleep diary (see Section 7.8).

3. Exploratory Outcomes

1. Actigraphy in relation to increasing doses of solriamfetol.

2. Differences in clinical activity of solriamfetol by treatment factors will be assessed by recording corticosteroid dose at baseline, antiepileptic use (presence/absence of prescribed antiepileptic and dose at baseline), and tumor grade by World Health Organization (WHO) criteria.

7 Treatment Plan

1. Overview of Treatment Plan

This is a single-arm, open label, two-part safety study of solriamfetol in patients with WHO grade 2-4 gliomas. Patients with stable disease by clinical examination and neuroimaging who have an ESS$\geq$10 and meet all inclusion/exclusion criteria will be recruited and enrolled. First, all patients will receive solriamfetol at escalating doses. Second, all patients will complete a fixed dose drug continuation treatment at the patient-specific maximum tolerated dose.
The study will occur in 3 phases:

1. Pre-Treatment Baseline (~1 week)

2. Flexible Dose Titration (~3 weeks)

3. Fixed Dose Drug Continuation (~6 weeks)

Patients will initially complete a 1-week baseline actigraphy and sleep diary prior to treatment initiation to establish a baseline sleep pattern.

Solriamfetol will be dosed by flexible dose titration starting at 75 mg daily in all patients and escalating after 7 days (1 week) to 150 mg daily and then after 7 days to 300 mg daily for a total duration of 3 weeks (flexible dose titration period). Patients who experience a dose-limiting toxicity will be de-escalated to the last tolerated dose level and move to the fixed dose drug continuation phase. Prior studies incorporating this design have used a 3-day treatment prior to escalation.[49] For this study, 7 days has been selected to provide a sufficient period of time to observe both immediate and delayed toxicities that could be seen in this population.

Following completion of the flexible dose titration, patients will continue solriamfetol at 300 mg daily or their maximally tolerated dose for a treatment duration of 6 weeks. For this period of the study, 8 weeks has been selected to allow for time to observe both short term improvement in patient-reported sleep as well as potentially more delayed changes in other study endpoints (i.e. fatigue, mood, neurocognition).

The main study assessments will be performed at baseline prior to flexible dose titration and then at the end of the fixed dose drug continuation phase. This will include: (1) patient reported measures, (2) objective measures of sleep activity, (3) neurocognitive functioning (4) assessment of associated symptoms such as fatigue, mood, and (5) quality of life. Additional assessment of patient-reported measures will be performed after dose escalation and prior to the fixed dose drug continuation. Due to practice effects and other issues related to repeated measurement, neurocognitive data will only be collected pre- and post-treatment.

Sleep diaries will be completed continuously throughout the ~10 week study. Seven-day actigraphy will be completed at each dose escalation and during the first and last weeks of fixed dose drug continuation.

Additional assessments will be performed as per the standard of care. In this population, it is standard of care for MR Brain to be performed roughly every 8-16 weeks. Data on tumor status by imaging (e.g. stable disease, imaging progression, etc) will be recorded prior to study treatment and following study treatment to assess for tumor progression as a factor contributing to changes in patient-reported and clinician assessed outcome measures.

Adverse events will be assessed every 7 days during flexible dose titration (via telephone) and at the end of the fixed dose treatment. Adverse event data will be compared to that reported in patients with narcolepsy.[50]

2. Study-Related Activities

	Pre-Study[a, k]	Baseline Visit V1 (D1)	Begin Flexible Dose Titration (D8+1 dy)	Flexible Dose D7 (D15+1 dy)	Flexible Dose D14 (D22+1 dy)	Fixed Dose Initiation Visit V2[k] (D29+7 dys)	End of Treatment Visit V3 (D70+7 dys)	30 day Follow Up Visit V4[k]
Informed consent	X							
Demographics	X							
Medical history	X							
Concurrent meds	X					X	X	
Physical exam[1]		X				X	X	X
Vital signs[b]	X[c]	X				X	X	X
CBC w/diff, platelets	X					X	X	X
Serum chemistry[d]	X					X	X	X
B-HCG[e]	X							
Electrocardiogram (EKG)		X				X		
Adverse event evaluation		X	X[f]	X[f]	X[f]	X	X	X
Epworth Sleepiness Scale (ESS)	X	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	
Sleep Measures: Sleep diary, Actigraphy[h]		X[i]	X	X	X	X	X	
Pittsburgh Sleep Quality Index (PSQI)		X				X	X	
Associated Symptom PROMs: BFI, CFS, BDI		X				X	X	
QOL PROMs: FACT-Br		X				X	X	
Neuro-cognitive Battery		X					X	
Standard of Care MR Brain[a]	X						X[j]	

[1] Patient's undergoing telehealth assessment at the pre-screening timepoint require virtual examination by observation only. Blood draw and laboratory testing can be performed locally and reviewed remotely.
[a] Pre-study requirements listed in table must be completed **within** 21 days prior to registration.
[b] Blood pressure (mmHg), heart rate (BPM)
[c] Height, Weight, M^2 Patients undergoing telehealth assessment can provide this information verbally using home device (e.g. scale).
[d] Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT[AST], SGPT[ALT], sodium.
[e] Serum pregnancy test (women of childbearing potential).
[f] May be performed by telephone.
[g] Epworth Sleepiness Scale (ESS) will be completed either in the clinic (D1, D29, D70) at each of the study visits (V1, V2, V3) or by telephone (D8, D15, D22) during the flexible dose escalation portion of the study.
[h] 7-day sleep diary is to be completed at baseline (D1-7), continuously during dose escalation (D8-14, D15-21, D22-28), and during the first and last week of fixed dose drug continuation (~D29-35 and ~D63-70). Actigraphy will be collected continuously.
[i] Patients may complete the baseline sleep diary and actigraphy prior to the Baseline Visit (V1) or after the Baseline Visit (V1).
[j] Post-treatment MR Brain is to be performed D85 $\pm$42 days.
[k] Study visits may be conducted via telehealth visit. Blood draw and EKG (when appropriate) can be performed locally and reviewed remotely.

3. Screening

Glioma patients seen at the Wake Forest Baptist Medical Center will be considered for eligibility at or before their scheduled visits. In general, patients may be approached at the time of routine outpatient visit for follow up with neuro-oncology, medical oncology, radiation oncology, and neurosurgery.

Patients who are identified as potential study candidates will have an opportunity to hear about the study and complete written informed consent. Patients who sign informed consent and do not meet eligibility criteria will be considered screen failures, will not be evaluable for the primary endpoint, will not count toward the total sample size, and this enrollment will be replaced.

Based on our prior cross-sectional study, we anticipate 30% of patients to be enrolled during adjuvant therapy (i.e. receiving oral chemotherapy), 30% during post-adjuvant surveillance (i.e. not receiving any prescribed antitumor therapy), and approximately 30% during post-recurrent disease treatment (i.e. undergoing salvage treatment with chemotherapy). This will allow for comparisons of toxicity, tolerability, and activity by timing during cancer care.

We anticipate that approximately 20-30% of patients will be taking active corticosteroids and 60% of patients will be prescribed an antiepileptic agent. This will allow us to explore differences in tolerability and activity by these important treatment parameters.

Screening assessments may be completed by telehealth visit. These will be done through MWH when able. If not able, Doximity will be used which is what is done clinically for these patients.

4. Pre-Treatment Baseline

All patients who complete written informed consent and meet eligibility criteria will be registered and will proceed with study treatment. For patients who complete consent at the time of a regularly scheduled visit they can be provided with a baseline sleep diary and actigraph device to complete the Pre-Treatment sleep diary and actigraphy prior to Visit 1 (V1). For patients who elect to take consider study enrollment and return at a later date, sleep diary and actigraphy can be completed after (in the first 7 days after) Visit 1 (V1).

Enrolled patients will complete the pre-treatment study assessments (Section 6.7). Patients will be instructed to complete a 1-week pre-treatment baseline assessment with 7-day sleep diary that records time in bed, time awake, and estimated hours of sleep among other items (Appendix Q) as well as 7-day actigraphy (see Section 7.8.2).

Patients will either return to clinic or receive a telephone call from the study nurse, study coordinator, or study team at the end of this pre-treatment baseline week (Day 7+1 day) to record the completion of pre-treatment baseline actigraphy and sleep diary.

Baseline visit will be performed in-person.

5. Flexible Dosing Titration

Upon completion of pre-treatment baseline assessments, patients will begin flexible dosing titration. All patients will begin solriamfetol 75 mg p.o. once daily. The dose will be titrated every

7 days (+1 day) to 150 mg daily and then 300 mg daily unless the patient experiences symptomatic dose-limiting toxicity.

Adverse events will be assessed by telephone call completed on D8+1 day, D15+1 day, and D22+1 day. Patients will be assessed in clinic at D29+7 days. Patients who report a symptomatic dose-limiting toxicity will de-escalate treatment back to the highest previously tolerated dose and will be seen for V2.

6. Fixed Dose Drug Continuation

At the completion of the flexible dose titration, patients will be seen for a routine study visit (V2) or via telehealth visit to document adverse events at the completion of flexible dosing, review sleep diary and actigraphy, and complete V2 assessments. Data from this interim time point may be used to clarify the trajectory of improvement, decline, and no change in study assessments. Patients will then proceed with fixed dose treatment at 300 mg p.o. once daily or the maximum tolerated dose for that patient.

Fixed dose drug continuation will be continued for 6 weeks. Patients will complete a sleep diary for the first 7 and last 7 days of fixed dose treatment; actigraphy will be collected continuously. At the completion of fixed dose treatment, patients will be seen for V3 study assessments (Section 6.7).

7. 30 Day Follow Up

All patients will be followed for 30 days following the completion of treatment to assess for delayed toxicity. Adverse events will be recorded at this 30 day follow up visit. If the patient is unable to return for this visit, adverse events will be recorded by telephone or telehealth visit.

8. Study Assessments

Assessment of sleep, neuro-cognitive function, fatigue, mood and quality of life will be assessed at baseline (V1) and at the end of the fixed-dose drug continuation phase of the study (V3). Given that patient drop out could occur during the course of the study treatment, study assessments that are not subject to significant practice and/or repeated measure effects will also be assessed after the flexible dose titration period (V2).

The following assessments will be performed:

1. Patient-reported outcome measures (PROMs) for sleep:

Changes in patient-reported outcomes measures (PROMs) are pivotal to cancer control drug approval.

The ESS is an 8-item validated instrument (min score 0 – max score 24, Appendix H) that is easy to implement and an accepted screening tool for symptoms of excessive daytime sleepiness. It has been well studied in patients with EDS and brain tumors.[7,13,45–47,51,52] An accepted cutoff of ESS≥10 has been used to indicate EDS for enrollment into studies evaluating therapeutic interventions.[50] Prior studies have indicated that a 25% reduction in ESS may be useful as a threshold to identify patients who respond to solriamfetol treatment.[53]

The PSQI is a 19-item validated self-report questionnaire (Appendix I) assessing sleep quality including subjective sleep quality, sleep latency, sleep duration, sleep efficiency,

and daytime dysfunction. Prior studies demonstrate impaired sleep quality in patients with cancer[40] and brain tumors.[52]

The ESS and PSQI measure non-overlapping orthogonal dimensions of self-reported sleep-wake symptoms.[52]

These measures will be completed prior to flexible dose titration, at the interim time point after flexible dose titration and before fixed dose continuation, and at end of treatment (see 7.2 Study-Related Activities).

2. Objective measures of sleep activity:

Actigraphy and sleep diaries are widely used, efficient, and affordable methods for measuring sleep-wake time.

Actigraphy has been shown to provide accurate data that is comparable to polysomnography[52] and is increasingly used to provide an objective measure of sleep in clinical trials.[52] Actigraph devices are worn on the wrist and record movements that can be used to estimate sleep patterns using specialized computer software programs. Completion of actigraphy will be recorded (Appendix R).

A 7-day sleep diary (Appendix R) will be provided to all patients at the time of consent and/or study enrollment. All sleep diaries will be collected over 7-days (i.e. 7-day sleep diary and 7-day actigraphy) including at pre-study baseline, throughout each dose of the dose escalation phase, and during the first 7-days and last 7-days of the fixed dose drug continuation phase of the study. Caregivers may complete sleep diaries for patients. Actigraphy will be collected continuously from baseline to end of treatment (see 7.2 Study-Related Activities).

3. Neurocognitive Battery:

The table below outlines the assessment measures that will be used to evaluate attention, concentration, information processing speed, learning/memory, and aspects of higher-order executive functions. These measures were selected in accordance with previously established standards for cognitive assessment with brain tumor patients and many are used in our own multidisciplinary clinic.[54–56] The protocol was modified slightly based on the skills most commonly identified as problematic for patients struggling with sleep disturbance and fatigue (attention/concentration and processing speed).

All proposed measures have adequate psychometric properties and most have been utilized in large national and international clinical oncology trials.[57,58] Alternate forms of the measures will be used to reduce practice effects where possible though some measures are less sensitive to such effects and do not have alternate forms (Digit Span, Letter Number Sequencing, etc.).

Neuropsychological changes will be assessed on an individual basis though a reliability change index (RCI) can also be obtained to allow an objective measure of change in the measured skill.

The following measures will be used:

Test Name:	Skill Measured:	Alternate Versions:	Time to Administer:
Digit Span (DS)	Basic rote attention span	NA	5-10 minutes
Letter Number Sequencing (LNS)	Complex working memory	NA	5-10 minutes
Matrix Reasoning (MR)	Visual abstract reasoning	NA	15-20 minutes
Symbol Search (SS)	Speeded symbol discrimination	NA	2-3 minutes
Coding (CD)	Clerical speed and accuracy	NA	2-3 minutes
Controlled Oral Word Association Test (COWAT)	Lexical and semantic verbal fluency and executive control	2 forms	6 minutes
Trail Making Test Parts A and B (TMT A & B)	Attention, processing speed, and cognitive set shifting	NA	6 minutes
Montreal Cognitive Assessment (MoCA)	Global cognitive functioning	3 forms	15 minutes
Total			50 – 65 minutes

This battery will be completed at V1 and V3 only (see 7.2 Study-Related Activities). This will not be performed at the interim V2 time point due to concern with practice effects and limited alternate forms for many of these assessments.

4. Patient-Reported Associated Symptoms:

Sleep disturbances co-occur with symptoms of fatigue and impaired mood in patients with brain tumors. Furthermore, improvement in any one of these symptom domains can have downstream effects on the other.

To assess fatigue, the Brief Fatigue Inventory (BFI) and Cancer Fatigue Scale (CFS) will be used (Appendix J & K). The BFI is a 9 item self-administered patient-reported questionnaire exploring the severity of fatigue and interference on life over the past 24 hours.[59–61] The Cancer Fatigue Scale is a 15-item self-administered patient-reported questionnaire exploring both overall and domain specific fatigue in cancer patients. The instrument explores three fatigue domains: physical effects of fatigue, cognitive effects, and affective issues related to cancer fatigue.[62] The combination of these instruments provides both a unidimensional (BFI) and multidimensional (CFS) assessment of fatigue. The CFS domains will allow us to also explore whether there might be differential effects on physical fatigue or cognitive aspects of fatigue compared to the affective factors. The BFI and CFS have robust psychometric properties, have been validated in cancer patients, and were recently reviewed in the American Society of Clinical Oncology Patient-Reported Outcomes (PRO) Recommendations.[42,43,60]

To assess depression, the Beck's Depression Inventory will be used (Appendix L). The BDI is a commonly employed measure of depressive symptoms and has been validated in cancer patients.[63,64] A cutoff of BDI$\geq$10 is often employed.[65]

These measures will be completed at V1, V2, and V3 (see 7.2 Study-Related Activities).

5. Quality of Life:
The Functional Assessment of Cancer Therapy (FACT) questionnaires are commonly used to assess cancer-related quality of life (Appendix N). The FACT-Brain (FACT-Br) provides an additional set of disease-specific questions pertaining to brain neoplasms and is commonly used in brain tumor studies to evaluate disease-specific quality of life.[65]

The FACT-Br will be assessed at V1, V2, V3 (see 7.2 Study-Related Activities).

9. Treatment Administration

Treatment will be administered on an outpatient basis. The study drug is to be taken orally once daily at approximately the same time each day. Each dose administered is to be recorded in the drug diary (Appendix F-G).

Reported adverse events and potential risks are described in Section 10.0. Appropriate dose modifications for are described in Section 8.0.

1. Definition of Dose-Limiting Toxicity (DLT)

A DLT is defined as a clinically-significant AE or abnormal laboratory value assessed as unrelated to disease progression, intercurrent illness, or concomitant medications and which meets any of the criteria below. Based on the prior studies of solriamfetol in patients with narcolepsy and obstructive sleep apnea, treatment is anticipated to be safe at all doses. In the prior phase 2a study, no patient had to discontinue the study treatment due to a treatment-related DLT.[47] In the prior phase 2b study, in patients who experienced an AE requiring discontinuation of solriamfetol, the AEs were not deemed to be related to the study medication. In the prior phase 3 study, 9 patients (9%) including one in the 75 mg arm, 3 in the 150 mg arm, and 5 in the 300 mg arm required discontinuation due to treatment related AEs.[45]

In prior studies, common adverse events include that have not required dose medication include headache (9-16%), nausea (12-14%), diarrhea (11%), decreased appetite (6-14%), anxiety (6-11%), chest discomfort (9%), insomnia (6%), muscle tightness (6%), nasopharyngitis (5-14%), and dry mouth (5-10%).

For this study, treatment-related DLTs are defined below. Dose limiting toxicities must have an attribution of possible, probable, or definite to solriamfetol. For patients experiencing a DLT during the dose escalation period, solriamfetol will be held. If the patient recovers (≤ grade 1 [or tolerable grade 2 for non-hematologic toxicity] or ≤ baseline), a dose reduction (1 dose level reduction) is required. The patient will proceed with 7-days of drug treatment at the new dose level and reassessed. If there is no evidence of AE then the patient will proceed to the fixed dose drug continuation phase of the study at that dose.

If there is any question or clarification required concerning a potential DLT, the treating clinician should contact the Study Chair to determine the patient's DLT status. The Study Chair will make the final decision.

- **Hematological toxicities** are not expected with this agent, must NOT be attributed to another source, and will be considered dose limiting only if any of the following occur and are probably or definitely attributed to solriamfetol:
    - ANC of < 500/mm3
    - Platelets < 25,000/mm3
    - Febrile neutropenia

      Note: Grade 3 or 4 lymphopenia will not be considered a DLT.
- **Central nervous system toxicities** will be considered dose limiting only if any of the following occur:
    - ≥ Grade 2 central nervous system (CNS) ischemia will be considered a DLT
    - ≥ Grade 2 neurological toxicities that interfere with activities of daily living and do not resolve spontaneously with steroids, anticonvulsants, or electrolyte correction within 7 days will be considered a DLT
    - Symptomatic CNS hemorrhage of any grade will be considered a DLT
    - ≥ Grade 3 seizure only if the patient requires inpatient hospitalization for medical intervention. A breakthrough seizure that is managed with minor antiepileptic drug modification will not be considered a DLT. Contact the Study Chair for clarification as needed.

- **Grade 3 and 4 non-hematological, non-CNS toxicities** will be considered dose limiting with the following exceptions:
    - Grade 3 nausea, vomiting, or diarrhea without sufficient prophylaxis with a duration <3 days
    - Insomnia
    - Alopecia
    - Fatigue
    - Grade 3 hyperglycemia that is reversible and without clinical symptoms
    - Grade 3 electrolyte disturbances that are asymptomatic and reversible within 3 days, and do not re-occur upon continuing or re-initiation at the same dose
    - Grade 3 or 4 hypophosphatemia, unless considered clinically relevant
    - Grade 3 or 4 elevations in alkaline phosphatase
    - Grade 3 hypertension unless inpatient hospitalization is required
    - A subject's first episode of deep venous thrombosis (DVT) or pulmonary embolism will not require dose modification

For patients who have begun the fixed dose drug continuation phase and experience a new dose-limiting toxicity, the study medication will be held until the DLT has resolved. If the DLT resolves within 14 days, the patient may resume therapy at the prior dose level (1 dose level reduction). If an additional dose reduction is required, the study medication should be discontinued.

Dose escalation will proceed for each patient according to the following scheme:

Dose Level	***Solriamfetol***
+1	*75 mg, p.o. once daily*
+2	*150 mg, p.o. once daily*
+3	*300 mg, p.o. once daily*

For patients who experience a dose limiting toxicity, the study drug will be de-escalated to the last tolerated dose. For patients who experience a dose-limiting toxicity at dose level +1, treatment will be discontinued and the patient will not receive further treatment.

2. Other Agent(s)

While receiving study drug treatment, patients may continue to receive tumor-directed chemotherapy, targeted therapy, or immunotherapy. Patients who are undergoing treatment with any of these tumor-directed treatments and who meet the eligibility criteria for the study will be able to continue to receive their anti-cancer therapy throughout the duration of the study as long as there is no known drug-drug interaction between the study drug and anti-cancer therapy.

3. Other Modality(ies) or Procedures

Patients who are anticipated to undergo surgery or radiation therapy are not permitted to receive the study drug as the safety profile has not been defined in the perioperative setting or when administered with radiation.

10. General Concomitant Medication and Supportive Care Guidelines

Patients should receive *full supportive care*, including transfusions of blood and blood products, erythropoietin, antibiotics, antiemetics, etc., as clinically indicated. Anti-inflammatory or narcotic analgesics may be offered as needed. Medications considered necessary for the patient's well-being may be given at the discretion of the investigator, i.e., chronic treatments for concomitant medical conditions, as well as agents required for life-threatening medical problems, etc. The reason(s) for treatment, dosage, and dates of treatment should be recorded on the flow sheets.

It is recommended that patients not be started on a new selective serotonin reuptake inhibitor (SSRI) or serotonin norepinephrine reuptake inhibitor (SNRI). Exception will need approval from the Study Chair. Patients taking sedative medications or other agents known to interact with sleep such as narcotics, benzodiazepines, antipsychotics, melatonin or other agents can be continued during the study. The doses of these medications should remain the same throughout the active treatment period of the study unless there is a medical indication for dose adjustment which will be determined by the patient’s treating physician. Corticosteroids should not be initiated unless medically indicated during the active treatment period. All changes in doses and new sedative medications, sleep active agents, or corticosteroids should be tracked including over-the-counter medications such as Tylenol PM, Benadryl, etc.

11. Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue for the duration of the study treatment (D70 +7 days) or until one of the following criteria applies:

- Disease progression requiring surgery or radiation therapy,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

12. Duration of Follow Up

Patients will be followed for a minimum of 30 days after the last study drug is administered for adverse events monitoring.

13. Determination of Evaluable Patients

Patients who enroll in the study but do not take a dose of the study medication will not be considered evaluable and will be replaced. In other words, patients who begin the pre-treatment baseline assessment and do not take the study medication will not be evaluable and will be replaced.

14. Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in section 5.4 applies.

8 Dosing Delays/Dose Modifications

During the flexible dose titration period of this study, dose modifications will be performed according to the Dose-Limiting Toxicity scheme outlined in Section 6.9.1.

During the fixed dose drug continuation period of this study, for patients who experience a new dose-limiting toxicity (see Section 6.9.1) treatment dose will be modified according to the following scheme:

Dose Level	***Insert Agent Name* Dose**
+1	*75 mg, p.o. once daily*
+2	*150 mg, p.o. once daily*
+3	*300 mg, p.o. once daily*

All dose modifications will be recorded, tracked and monitored via a drug diary (Appendices F and G) throughout the duration of study treatment.

9 Measurement of Effect

Tumor response and survival outcomes will NOT be included as an endpoint in this study. MRI Brain is included to track evidence of clinically documented progressive disease which could contribute to changes in patient-reported and clinician assessed outcome measures (see Section 7.8).

10 Adverse Events List and Reporting Requirements

1. Adverse Event List for solriamfetol

In the 12-week placebo-controlled studies in patients with narcolepsy and OSA, in the overall population the most frequent (≥5%) adverse events that also had a higher incidence with solriamfetol than with placebo were:

- Headache (11-21%)
- Nausea (8-11%)
- Decreased appetite (8-11%)
- Anxiety (6-7%)
- Diarrhea (5-6%)
- Dry mouth (5-6%)
- Insomnia (5-8%)

Less common adverse events occurring at a rate of ≥1% in the combined solriamfetol treatment group and higher than the placebo rate are shown in Table 2.

Patients with OSA who completed either of the two 12 –week placebo-controlled clinical trials, as well as patients with narcolepsy who completed a previous clinical trial of solriamfetol in the treatment of excessive sleepiness were eligible to participate in a study to evaluate the long-term safety and maintenance of efficacy of solriamfetol. The most common Treatment Emergent Adverse Events (TEAEs, ≥ 5% in combined solriamfetol groups for any indication) in the safety population across the entire study were:

- Headache (11%)
- Nausea (8.9%)
- Insomnia (7.9%)
- Nasopharyngitis (8.4%)
- Dry mouth (7.3%)
- Anxiety (7.2%)
- Decreased appetite (5.0%), and
- Upper respiratory tract infection (5.0%)

Serious TEAEs were reported in 27 (4.2%) patients across all phases. There were a total of 9 patients with 9 cardiovascular or potential cardiovascular serious TEAEs:

- 2 cases of atrial fibrillation
- 1 case of acute myocardial infarction
- 1 case of angina pectoris
- 1 case of chest discomfort

- 1 case of chest pain
- 1 case of non-cardiac chest pain
- 1 case of cerebrovascular accident, and
- 1 case of pulmonary embolism

There was one death due to sepsis, which occurred in a 70-year old immunosuppressed male with OSA on SUNOSI 300 mg. The death was considered unrelated to study drug by the investigator.

Table 2: Common Adverse Drug Reactions in the 12-Week Placebo-controlled Parallel Group Studies in Narcolepsy and Obstructive Sleep Apnea Overall and by Indication (Safety Population)

System Organ Class Adverse Reaction, n (%)	Narcolepsy & OSA		Narcolepsy		OSA	
	Placebo (N=226)	Combined solriamfetol (N=573)	Placebo (N=108)	Combined solriamfetol (N=220)	Placebo (N=118)	Combined solriamfetol (N=353)
Cardiac Disorders						
Palpitations	1 (<1.0)	14 (2)	1 (<1.0)	6 (3)	0	8 (2)
Gastrointestinal Disorders						
Nausea	11 (5)	53 (9)	4 (4)	25 (11)	7 (6)	28 (8)
Diarrhea	5 (2)	30 (5)	4 (4)	13 (6)	1 (<1.0)	17 (5)
Dry Mouth	4 (2)	29 (5)	2 (2)	13 (6)	2 (2)	16 (6)
Abdominal Paina	5 (2)	18 (3)	3 (3)	6(3)	2 (2)	12 (3)
Constipation	2 (<1.0)	12 (2)	1 (<1.0)	6 (3)	1 (<1.0)	6 (2)
Vomiting	2 (<1.0)	6 (1)	1 (≤1.0)	2 (<1.0)	1 (<1.0)	4 (1)
General Disorders and Administration Site Conditions						
Feeling Jittery	0	17 (3)	0	3 (1)	0	14 (4)
Chest discomfort	0	10 (2)	0	1 (<1.0)	0	9 (3)
Investigations						
Heart rate increased	0	8 (1)	0	5 (2)	0	3 (<1.0)
Blood Pressure increased	1 (<1.0)	7 (1)	1 (<1.0)	3 (1)	0	4 (1)
Weight decreased	0	7 (1)	0	5 (2)	0	2 (<1.0)
Metabolism and Nutrition Disorders						
Decreased appetite	2 (<1.0)	52 (9)	1 (<1.0)	25 (11)	1 (<1.0)	27 (8)
Nervous System Disorders						
Headacheb	18 (8)	84 (15)	8 (7)	46 (21)	10 (8)	38 (11)
Dizziness	4 (2)	19 (3)	3 (3)	9 (4)	1 (<1.0)	10 (3)
Psychiatric Disorders						
Anxiety	1 (<1.0)	39(7)	1 (<1.0)	14 (6)	0	25 (7)
Insomniac	7 (3)	33 (6)	4 (4)	17 (8)	3 (3)	16 (5)
Irritability	1 (<1.0)	13 (2)	1 (<1.0)	5 (2)	0	8 (2)
Bruxism	0	8 (1)	0	4 (2)	0	4 (1)
Agitation	1 (<1.0)	7 (1)	0	4 (2)	1 (<1.0)	3 (<1.0)
Respiratory, Thoracic and Mediastinal Disorders						
Cough	0	10 (2)	0	3 (1)	0	7 (2)
Skin and Subcutaneous Tissue Disorders						
Hyperhidrosis	0	9 (2)	0	3 (1)	0	6 (2)
Vascular Disorders						
Hypertension	0	6 (1)	0	0	0	6 (2)

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 18.0.

Percentages are subject incidences based on N, number of subjects within each treatment group in safety population treated in 12-week randomized studies ADX-N05 202, 14-002 and 14-003.Common adverse reactions are those occurring at a rate of ≥1% in the combined JZP- 110 treatment group and higher than the placebo rate. Events occurring at a rate of >1% were rounded to the nearest whole percent. Events occurring <1% are noted as such.[a]Abdominal pain is a combined term of 'abdominal pain,' 'abdominal pain upper,' and 'abdominal discomfort.[b]Adverse reaction 'Headache' is a combined term of 'headache,' 'tension headache,' and 'head discomfort.[c]Insomnia' is a combined term of 'insomnia,' 'initial insomnia,' 'middle insomnia,' and 'terminal insomnia.

Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

- **'Expectedness'**: AEs can be 'Unexpected' or 'Expected' (see Section 7.1 above) for expedited reporting purposes only.

- **Attribution** of the AE:

- Definite – The AE **is clearly related** to the study treatment.
- Probable – The AE **is likely related** to the study treatment.
- Possible – The AE **may be related** to the study treatment.
- Unlikely – The AE **is doubtfully related** to the study treatment.
- Unrelated – The AE **is clearly NOT related** to the study treatment.

2. DSMC SAE Reporting Requirements

The Data and Safety Monitoring Committee (DSMC) is responsible for reviewing SAEs for WFBCCC Institutional studies as outlined in Appendix B. DSMC currently requires that all unexpected 4 and all grade 5 SAEs on these trials be reported to them for review. All WFBCCC Clinical Research Management (CRM) staff members assisting a Principal Investigator in investigating, documenting and reporting an SAE qualifying for DSMC reporting are responsible for informing a clinical member of the DSMC as well as the entire committee via the email notification procedure of the occurrence of an SAE.

3. WFUHS IRB AE Reporting Requirements

Any unanticipated problems involving risks to subjects or others and adverse events shall be promptly reported to the IRB, according to institutional policy. Reporting to the IRB is required regardless of the funding source, study sponsor, or whether the event involves an investigational or marketed drug, biologic or device. Reportable events are not limited to physical injury, but include psychological, economic and social harm. Reportable events may arise as a result of drugs, biological agents, devices, procedures or other interventions, or as a result of questionnaires, surveys, observations or other interactions with research subjects.

All members of the research team are responsible for the appropriate reporting to the IRB and other applicable parties of unanticipated problems involving risk to subjects or others. The Principal Investigator, however, is ultimately responsible for ensuring the prompt reporting of unanticipated problems involving risk to subjects or others to the IRB. The Principal Investigator is also responsible for ensuring that all reported unanticipated risks to subjects and others which they receive are reviewed to determine whether the report represents a change in the risks

and/or benefits to study participants, and whether any changes in the informed consent, protocol or other study-related documents are required.

Any unanticipated problems involving risks to subjects or others occurring at a site where the study has been approved by the WFUHS IRB (internal events) must be reported to the WFUHS IRB within 7 calendar days of the investigator or other members of the study team becoming aware of the event.

Any unanticipated problems involving risks to subjects or others occurring at another site conducting the same study that has been approved by the WFUHS IRB (external events) must be reported to the WFUHS IRB within 7 calendar days of the investigator or other members of the study team becoming aware of the event.
Any event, incident, experience, or outcome that alters the risk versus potential benefit of the research and as a result warrants a substantive change in the research protocol or informed consent process/document in order to insure the safety, rights or welfare of research subjects.

4. Sponsor Reporting Requirements

WFBMC will and will ensure that the Investigator complies with Applicable Law in connection with the study, including but not limited to providing all adverse drug experience reports and notifications by the relevant Governmental Authority.

All serious adverse events that require reporting per the Protocol and which occur in a subject wo received the Product as part of the study will be reported by email (AEreporting@jazzpharma.com) to Jazz Pharmaceuticals not later than 1 buisness day following WFBMCs receipt of notice of such occurrence. In addition, WFBMC will ensure that the Investigator provides a copy of all final reports regarding such adverse events that are provided by WFBMC or Investigator to the relevant Governmental Authority, which reports will be provided by email (PVcomms@jazzpharma.com) to Jazz Pharmaceucitcals at the time of submission to the Governmental Autorhity. All other adverse events will be reported to Jazz Pharmaceuticals (PVcomms@jazzpharma.com) in summary or line-item form upon written request and at the conclusion of the study.

11 Pharmaceutical Information

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 9.0.

1. Pharmaceutical Accountability

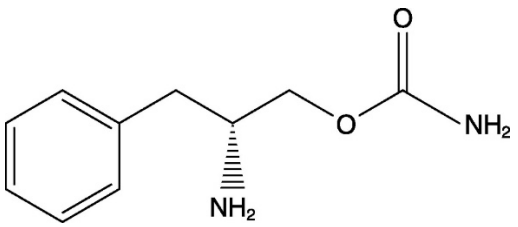
Drug accountability logs will be maintained for all agents used under this protocol. These logs shall record quantities of study drug received and quantities dispensed to patients, including lot number, date dispensed, patient identifier number, patient initials, protocol number, dose, quantity returned, balance remaining, and the initials of the person dispensing the medication.

2. Solriamfetol [44]

Chemical Name: (*R*)-2-amino-3-phenylpropylcarbamate hydrochloride

Other Names: JZP-110, ADX-N05.

Chemical Structure:



Pharmaceutical Properties: solriamfetol is a late-stage investigational wakefulness promoting agent in clinical development for the treatment of excessive daytime sleepiness (EDS) in adult patients with conditions including narcolepsy or obstructive sleep apnea. Solriamfetol is a phenylalanine derivative with dopaminergic and noradrenergic activity. Its mechanism of action, although not fully determined, includes low potency dopamine and norepinephrine reuptake inhibition.[44] It is distinct from modafinil and traditional stimulants used in patients with EDS.

Formulations: solriamfetol is formulated as an immediate release tablet available in 75 mg, 150 mg, and 300 mg strengths. The agent is supplied by Jazz Pharmaceuticals, INC. Packaging?

Route of Administration: Oral, given with or without food. Each dose should be taken with 8 ounces (240 mL) of water.

Storage Requirements: solriamfetol tablets are to be stored at room-temperature conditions, 15°C to 30°C (59°F to 86°F).

Stability: Studies are ongoing to monitor the stability of solriamfetol tablets.

12 Data Management

Informed consent document	EPIC
Protocol registration form	OnCore
Adverse Events Log (Appendix E)	OnCore
Patient Drug Diary (Appendix F)	
Fixed Dose Patient Drug Diary (Appendix G)	
Epworth Sleepiness Scale (Appendix H)	
Pittsburgh Sleep Quality Index (Appendix I)	
Brief Fatigue Inventory (Appendix J)	
Cancer Fatigue Scale (Appendix K)	
Beck's Depression Inventory (Appendix L)	
Neurocognitive Battery Form (Appendix M)	
FACT-Br (Appendix N)	
Concurrent Medication (Appendix O)	OnCore
Off-Study Form (Appendix P)	OnCore
MR Imaging Record (Appendix Q)	
Sleep Diary and Actigraphy Record (Appendix R)	
Glioma History (Appendix S)	

13 Statistical Considerations

This is a single-arm, open label, non-randomized safety study in patients with stable glioma disease. The primary outcome is safety of oral solriamfetol as doses of 75 mg daily, 150 mg daily and 300 mg daily. Secondary outcomes include ESS score, PSQI score, a composite neurocognitive battery score, FSS score, BDI score, and FACT-Br score.

1. Analysis of Primary Objective

For the primary outcome, NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be used for scoring toxicity and adverse events.

The severity and frequency of toxicity and adverse events for each dose of solriamfetol will be tabulated using descriptive statistics. The proportions of subjects who experienced grade 3 or above toxicities will be estimated, along with 95% confidence intervals by each type of toxicity.

To compare the safety of solriamfetol at 75 mg daily, 150 mg daily, 300 mg daily, chi-squared statistics will be used. If there are some cells with expected value <5, Fisher's exact test will be used for the comparison.

2. Analysis of Secondary Objective

For the secondary outcomes, descriptive statistics will be performed for each of the outcome measures. Changes in pre- and post-treatment scores will be assessed and compared using the pair-t tests if the changes follow a normal distribution and using the Wilcoxon signed rank tests if the changes do not follow a normal distribution. For the comparison between the change in ESS score in the study patients and the published change score in patients with obstructive sleep apnea, we will use the one sample t-test for this comparison.

3. Analysis of Exploratory Objective

13.3.1 To explore the dose response effect of solriamfetol on actigraphy, linear regression models will be used where the dosage will be treated as an ordinal variable. Transformation of actigraphy will be performed to satisfy the normality assumption if needed.

13.3.2 The analysis will be the same as that specified in 13.1.

4. Power and Sample Size

We plan to recruit around 36 participants.

In the prior phase 2a and phase 2b studies in patients with narcolepsy which had similar sample sizes, no patients in the phase 2a and three patients in the phase 2b study required discontinuation of study medication, though two of these discontinuations were not attributed to the study drug.[46,47] In the prior phase 3 study, 9 patients (9%) including one in the 75 mg arm, 3 in the 150 mg arm, and 5 in the 300 mg arm required discontinuation due to treatment related AEs.[45] In the current study, 36 patients will receive 75 mg daily dosing. We conservatively estimate that at least 33 patients will escalate to 150 mg daily, and at least 30 patients will escalate to receive 300 mg daily. These estimates are felt to be overly conservative based on data from these prior studies in patients narcolepsy.

From prior studies, the most common adverse event proportions range from 10% to 20%. Assuming 10% and 20% of adverse event proportion, the detectable proportions for the combined dosage are 24% and 36%, respectively, in order to reach 80% power at a significance level of 0.1 (given the pilot nature of this study) and a two-sided test. These detectable proportions are reasonable. If we observe an adverse event proportion in the patients with primary gliomas that is higher than 36%, then the adverse event proportion is significantly higher than the other study populations. In practice, if an adverse event proportion is higher than 50%, then the safety/tolerability of solriamfetol needs to be questioned. We should have enough power for this primary analysis. Note that this study allows us to determine safety profiles for the 3 doses of solriamfetol. It is primarily for descriptive purpose and to generate data on safety and estimation of effect size for the design of a subsequent randomized study powered to determine drug activity. The results generated from this study will be beneficial for the future research study.

ESS score is the most important secondary outcome in this study. We also calculate the power to test whether the pre-post change is different from 0 and test whether the change is different from the pre-post change in the prior studies which recorded the pre-post changes for patients at 75 mg, 150 mg, and 300 mg. At an alpha of 0.10, a two-sided test, and cohort sample size of 36 patients, the study will have 80% power to detect the mean difference of 1.01 point (=0.42 standard deviation (SD)) in ESS score from the study sample. The mean differences are reasonable. We should have enough power for our analysis.

Prior studies of solriamfetol in patients with narcolepsy have demonstrated improvement in ESS scores at Week 8 of -3.4 (75 mg daily), -5.2 (150 mg daily), -6.4 (300 mg daily), and -2.1 (placebo) with baseline ESS ranging from 16.9-17.3. In patients with OSA, Week 8 improvements were -6.3 (75 mg daily), -6.9 (150 mg daily), -7.7 (300 mg daily), and -3.8 (placebo) in patients with baseline ESS ranging from 14.8 to 15.6. In our prior study mean ESS score for patients with primary brain tumors who would be eligible for the proposed study (i.e. ESS$\geq$10) was 14.8 (SD: 2.4). For the current study, we will use the data from the prior OSA study as a comparator given that baseline ESS scores were similar to what we anticipate in the to-be-enrolled cohort. Based on this, the study hypothesizes that treatment with solriamfetol at 75 mg, 150 mg, or 300 mg will achieve at least a 6.3 point difference (75 mg daily) and up to 7.7 point different (300 mg daily) in ESS scores at Week 10 (baseline vs V3). This will be compared to a null difference of 3.8 (placebo arm in OSA study). This mean change in ESS scores is clinically meaningful as has been reported.[53] In order to detect the differences between the mean change ESS score from the proposed study to the mean change of 3.8 in the placebo arm in OSA study, the detectable mean change needs to be greater than 5.4 in the study sample in order to reach 80% power. We hypothesize that the mean change in this study sample ranges from 6.3 to 7.7, which is higher than 5.4. We should have sufficient power to detect the difference between the mean change ESS score in our study sample and that in the placebo arm in the OSA study.

5. Estimated Accrual Rate

The target population includes WHO Grade 2, Grade 3, and Grade 4 gliomas. The median survival for each of these tumors is approximately 10-15 years, 2-7 years, and 20 months, respectively. WHO Grade 4 gliomas (median OS ~20 months) are included in this study to address the safety of this agent.

Ultimately, long term treatment could be most beneficial for those with WHO Grade 2-3 tumors where the sleep-fatigue symptom cluster is a significant problem for long term survivorship.

Furthermore, these pilot data will not only inform subsequent drug development of solriamfetol in this population but also in other cancer patients receiving or having completed chemo-radiotherapy, in neurologically diseased patients taking antiepileptics, or patients prescribed corticosteroids.

6. Estimated Study Length

Anticipated Enrollment Duration: 18 months

Anticipated Treatment Duration: 24 months (18 month enrollment + 6 month on and post-treatment follow up)

Total Study Duration from first patient enrollment to end: 2 years
Anticipated Patient Enrollment per month: 2

Total Anticipated Patient Enrollment: 36

7. Interim Analysis Plan

Interim analysis of safety data will be performed when all 36 evaluable patients have completed dose escalation. Interim analysis of secondary efficacy endpoints is not planned.

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Appendix A – Eligibility Checklist

IRB Protocol No.	**WFBCCC Protocol No.**
Study Title: Open Label Safety Study of Solriamfetol to Promote Wakefulness and Improve Cognition and Quality of Life in Patients with Primary Gliomas	
Principal Investigator: Roy Strowd, MD	

Inclusion Criteria (as outlined in study protocol)	**Criteria is met**	**Criteria is NOT met**	**Source Used to Confirm * (Please document dates and lab results)**
1 WHO Grade 2-4 infiltrating glioma by histologic confirmation • Where appropriate results from clinically available testing of isocitrate dehydrogenase (IDH) gene mutation status (for all gliomas), chromosome 1p and 19q deletion status (for suspected oligodendrogliomas), and MGMT gene promoter methylation status (for malignant gliomas) must be available in the patient's chart. • These studies are standard of care molecular studies that are performed as a part of routine clinical practice and allow for integrated molecular subtyping of primary glial tumors.	☐	☐	
2 Epworth Sleepiness Scale (ESS) score ≥10 within 21 days of enrollment	☐	☐	
3 Clinical and/or radiographic evidence of stable disease within 21 days of enrollment	☐	☐	
4 Patients must have completed ***concurrent*** chemoradiation with recovery of all pre-existing toxicity to CTCAE Grade >1 • Patient who are anticipated to undergo surgery and/or radiation therapy for management of their tumor during the duration of study treatment are NOT eligible. • Patients who are anticipated to undergo adjuvant chemotherapy are eligible as long as there is no evidence of tumor progression by clinical exam and/or imaging within 21 days of enrollment (see 4.1.2). This determination should be made by clinical documentation and if there is question discussed with the Study Chair. Adjuvant chemotherapy is not an exclusion. • Patients who are currently undergoing chemotherapy, targeted therapy, immunotherapy, or salvage treatment and have stable disease by imaging are eligible and can continue the current anti-cancer therapy. Patients who will require a new anti-cancer treatment or are anticipated to change anti-cancer treatments are not eligible.	☐	☐	
5 Age ≥ 18 years	☐	☐	
6 Karnofsky performance status ≥ 60%	☐	☐	
7 Life expectancy of greater than 4 months	☐	☐	
8 Patients must have normal organ and marrow function as defined below: • leukocytes ≥3,000/mcL • absolute neutrophil count ≥1,500/mcL • platelets ≥100,000/mcL • total bilirubin 1.5 X institutional ULN • AST(SGOT)/ALT(SGPT) ≤2.5 X institutional ULN • creatinine within normal institutional limits OR • creatinine clearance ≥50 mL/min/1.73 m^2 for Cre >ULN	☐	☐	

9	The effects of solriamfetol on the developing human fetus are unknown. For this reason women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately	☐	☐	
10	Ability to understand and the willingness to sign an IRB-approved informed consent document (either directly or via a legally authorized representative)	☐	☐	
	Exclusion Criteria (as outlined in study protocol)	**Criteria NOT present**	**Criteria is present**	**Source Used to Confirm * (Please document dates and lab results)**
1	Receiving active radiation therapy (including patients who are within 28 days of completing radiation therapy)	☐	☐	
2	Anticipated to undergo radiation therapy or require neurosurgical intervention during the period of active treatment (i.e. within the next 4 months)	☐	☐	
3	Contraindication to solriamfetol based on drug-drug interactions or concurrent systemic illness that precludes drug treatment	☐	☐	
4	Patients who have not recovered to <CTCAE grade 2 toxicities related to prior or current therapy are ineligible. • Exception for laboratory-based or other adverse event that is stable and not anticipated to interfere with study related treatment must be reviewed and approved by the Study Chair.	☐	☐	
5	Customary bedtime later than midnight	☐	☐	
6	Known and/or documented history of obstructive sleep apnea (OSA)	☐	☐	
7	Uncontrolled behavioral or psychiatric disorder (including suicidal ideation)	☐	☐	
8	Current excessive caffeine use (>600 mg/day or >6 cups of coffee/day)	☐	☐	
9	Current or prior history of alcohol or drug abuse within the last 2 years as assessed by the treating clinician	☐	☐	
10	Nicotine dependence that is currently interfering with sleep based on assessment by the treating clinician	☐	☐	
11	Concurrent use of selective serotonin or norepinephrine reuptake inhibitors (e.g. SSRI, SNRI) within 14 days of study enrollment • Patients who are currently taking these agents may be tapered at the direction of the treating physician prior to study enrollment. • Patients taking other medications such as narcotics, benzodiazepines, antipsychotics, antiepileptics, corticosteroids, or over-the-counter sleep aids can be enrolled. It is recommended that the doses of these medications remain the same throughout the portion of active study treatment unless there is a medical indication for dose adjustment which will be determined by the treating physician (see Section 7.10).	☐	☐	
12	History of allergic reactions attributed to compounds of similar chemical or biologic composition to solriamfetol	☐	☐	

13	Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements	☐	☐	
14	Pregnant women are excluded from this study because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with –solriamfetol, breastfeeding should be discontinued if the mother is treated with solriamfetol	☐	☐	

This subject is ☐ eligible / ☐ ineligible for participation in this study.

OnCore Assigned PID: _____

Signature of research professional confirming eligibility: _____ Date: _____

Signature of Treating Physician: _____ Date: _____

Signature of Principal Investigator**: _____ Date: _____

* Examples of source documents include clinic note, pathology report, laboratory results, etc. When listing the source, specifically state which document in the medical record was used to assess eligibility. Also include the date on the document. Example: “Pathology report, 01/01/14” or “Clinic note, 01/01/14”

**Principal Investigator signature can be obtained following registration if needed

Appendix B – Protocol Registration Form

DEMOGRAPHICS

Patient: Last Name: _____ First Name: _____

MRN: ___ ___ ___ ___ ___ ___ ___ ___ DOB (mm/dd/yy): ___ ___ / ___ ___ / ___ ___

ZIPCODE: ___ ___ ___ ___ ___

SEX: ☐ Male ☐ Female Ethnicity (choose one): ☐ Hispanic ☐Non-Hispanic

Race (choose all that apply): ☐ WHITE ☐BLACK ☐ ASIAN ☐ PACIFIC ISLANDER ☐ NATIVE AMERICAN

Height: ___ ___.___ inches Weight: ___ ___ ___.___lbs.(actual)

Surface Area: ___ ___.___m^2

Primary Diagnosis: _____

Date of Diagnosis: ___ ___ /___ ___/___ ___

Performance Status: ___ ___ ___ ☐ ECOG ☐ Karnofsky

PROTOCOL INFORMATION

Date of Registration: ___ ___ / ___ ___ / ___ ___

MD Name (last) : _____

Date protocol treatment started: ___ ___ / ___ ___ / ___ ___

Informed written consent: ☐ YES ☐ NO

(consent must be signed prior to registration)

Date Consent Signed: ___ ___ / ___ ___ / ___ ___

PID # (to be assigned by OnCore): ___ ___ ___ ___ ___ ___ ___ ___

Protocol Registrar can be contact by calling [redacted] between 8:30 AM and 4:00 PM, Monday – Friday.

Completed Eligibility Checklist and Protocol Registration Form must be hand delivered, faxed or e-mailed to the registrar at [redacted]

Appendix C - Race & Ethnicity Verification Form

Thank you so much for helping us to verify your race and ethnicity to ensure the quality of our information. As a brief reminder, the information you provide today will be kept confidential.

1. Are you:
   - ☐ Hispanic or Latino/a
   - ☐ Not Hispanic or Latino/a

2. What is your race? One or more categories may be selected.
   - ☐ White or Caucasian
   - ☐ Black or African American
   - ☐ American Indian or Alaskan Native
   - ☐ Asian
   - ☐ Native Hawaiian or Other Pacific Islander
   - ☐ Other, Please Specify: _____

Internal use only:

Name: _____ MRN#: _____

Was the self-reported race and ethnicity of the participant verified at the time of consent?
☐ **Yes** ☐ **No**

Was a discrepancy found? **Yes** ☐ **No** ☐
If yes, please provide what is currently indicated in the EMR:
Ethnicity: _____ Race: _____

Additional comments: _____
_____
_____

Appendix D – Mandatory DSMC SAE Reporting Guidelines

Data and Safety Monitoring Committee (DSMC) Serious Adverse Event (SAE) Notification SOP	**Date: 02/11/2021**

Mandatory DSMC SAE Reporting Requirements in WISER

This document describes reporting requirements of adverse events from **WFBCCC Investigator Initiated interventional trials to the Data and Safety Monitoring Committee (DSMC).** A trial is considered a **WFBCCC Investigator Initiated interventional trial** if the following criteria are met:

1) The Principal Investigator (PI) of the trial is a member of a department at the Wake Forest University Baptist Medical Center.
2) WFBCCC is considered as the primary contributor to the design, implementation and/or monitoring of the trial.
3) The trial is designated as "Interventional" using the Clinical Research Categories definitions provided by the NCI in the Data Table 4 documentation. (https://cancercenters.cancer.gov/GrantsFunding/DataGuide#dt4)

There are two distinct types of WFBCCC Investigator Initiated interventional trials based on where patient enrollment occurs. These include:

1) Local WFBCCC Investigator Initiated interventional trials defined as trials where **all patients are enrolled from one of the WFBCCC sites.** These include the main outpatient Cancer Center clinics (located in Winston-Salem) as well as WFBCCC affiliate sites located in Bermuda Run (Davie Medical Center), Clemmons, Lexington, High Point, or Wilkesboro.
2) Multi-Center WFBCCC Investigator Initiated interventional trials defined as trials where patients are enrolled from other sites in addition to WFBCCC sites. There are three types of trials that are included in this category:
    a. Trials sponsored by the NCI Community Oncology Research Program (NCORP) that are conducted at multiple sites where the PI is a member of a department at the Wake Forest University Baptist Medical Center.
    b. Trials sponsored by Industry that are conducted at multiple sites and the PI is a member of a department at the Wake Forest University Baptist Medical Center.
    c. Trials sponsored by WFBCCC that are conducted at multiple sites and the PI is a member of a department at the Wake Forest University Baptist Medical Center.

All Adverse Events (AEs) and Serious Adverse Events (SAEs) that occur on any patients enrolled on WFBCCC Investigator Initiated Interventional trials must be entered into the WISER system. The only exception to this requirement is for patients enrolled on NCORP trials at non- WFBCCC sites. AEs and SAEs for NCORP patients enrolled at WFBCCC sites must be entered into the WISER system. Once these AEs and SAEs are entered in WISER, certain actions must be taken regarding the reporting of specific Adverse Events to the DSMC.

All Adverse Events that occur during protocol intervention (defined below) and are coded as either 1) **unexpected grade 4,** 2) **unplanned inpatient hospitalization ≥ 24 hours (regardless of grade)**, or **grade 5 (death)** must be reported to the DSMC using the using the SAE console in WISER.

A research nurse or clinical research coordinator when made aware that an adverse event meets one of the above criteria has occurred on a WFBCCC Investigator Initiated interventional trial, is responsible for informing a clinical member of the DSMC by phone (or in-person) about the adverse event. The nurse/coordinator should contact the treating physician prior to calling the DSMC clinical member to obtain all details of the SAE, as well as all associated toxicities to be recorded along with the SAE. In addition, this nurse or coordinator is responsible for entering the adverse event information into the SAE console in WISER. Once the adverse event has been entered into the SAE console an email informing the entire DSMC will be generated.

THESE REPORTING REQUIREMENTS APPLY TO any staff member on the study team for a WFBCCC Institutional Interventional trial. Ultimately, the protocol PI has the primary responsibility for AE identification, documentation, grading and assignment of attribution to the investigational agent/intervention. However, when an AE event as described above is observed, it is the responsibility of the person who observed the event to be sure that it is reported to the DSMC.

What is considered during protocol intervention?
During protocol intervention is considered to be the time period while a patient is on study treatment or during the time period within 30 days of last study treatment (even if patient begins a new (non-study) treatment during the 30 days). This window of 30 days should be the standard window to be used in all protocols unless a specific scientific rationale is presented to suggest that a shorter window can be used to identify events. If it is a trial sponsored by Industry and the sponsor requires a longer window for monitoring of SAEs, then the longer window of time specified by the sponsor should be followed.

What is considered as an Unexpected Grade 4 event?

Any grade 4 event that was not specifically listed as an expected adverse event in the protocol should be considered as unexpected. A grade 4 adverse event can be considered to be unexpected if it is an event that would not be expected based on the treatment being received or if it is unexpected based on the health of the patient. In either case, if there is any uncertainty about whether a grade 4 adverse event is expected or unexpected it should be reported to DSMC.

DSMC notification responsibilities of the person (e.g., nurse) handling the reporting/documenting of the SAE in WISER:

1. Make a phone call (or speak in person) to the appropriate clinical member of the DSMC according to the schedule as listed below (page if necessary).
2. Enter a new SAE into the SAE module that is located in the Subject>> CRA Console in WISER WITHIN 24 HOURS of first knowledge of the event. Information can be entered and saved, but the DSMC members will not be notified until a date is entered into the DSMC Notification Date Field. This will ensure that all persons that need to be made aware of the event (i.e., PI, study team members and DSMC members) will be notified; remember to file a copy of the confirmation.
3. Document that the appropriate person(s) on the DSMC has been contacted. Indicate the name of the DSMC clinician that was contacted and the date and time contacted in the Event Narrative field in the SAE console of the particular subject.
4. Document whether or not the protocol should be suspended based on the discussion with the DSMC clinician. This is the major function of the email notification. Enter whether the protocol should be suspended in the Event Narrative Field.
5. Follow up/update the clinical member(s) of DSMC regarding any new developments or information obtained during the course of the SAE investigation and reporting process.

Elements needed to complete the SAE form in the Subject Console in WISER (see Screen Shot 3):

1. Event Date
2. Reported Date
3. Reported by
4. If Grade 5, enter Death Date
5. If Grade 5, enter Death occurred: within 30 days
6. Event Narrative: Brief description (include brief clinical history relevant to this event, including therapies believed related to event). Begin narrative with the DSMC clinician who was notified and Date/Time notified. In addition, state attribution by DSMC clinician as either “Unrelated”, “Unlikely”, “Possibly”, “Probably”, or “Definitely”. Always include the following here:
    i. DSMC clinician name, date/time contacted and comments

ii. Date of last dose before the event
iii. Is suspension of the protocol needed? Y/N

7. Treating Physician comments
8. PI comments, if available
9. Protocol Attribution after discussion with DSMC clinician
10. Outcome (Fatal/Died, Intervention for AE Continues, Migrated AE, Not Recovered/Not Resolved, Recovered/Resolved with Sequelae, Recovered/Resolved without Sequelae, Recovering and Resolving)
11. Consent form Change Required? Y/N
12. SAE Classification ***This is required in order for the email notification to be sent***
13. Adverse Event Details – Enter all details for each AE associated with the SAE.
    a. Course start date
    b. Category
    c. AE Detail
    d. Comments
    e. Grade/Severity
    f. Unexpected Y/N
    g. DLT Y/N
    h. Attributions
    i. Action
    j. Therapy
    k. Click ADD to attach the AE Detail to the SAE.
14. Enter Date Notified DSMC -- ***This is required for the email notification to be sent***
15. Click Submit. The auto-generated notification email will disseminate within 5 minutes. If you do not receive an email within 5 minutes, check that you have entered the "Date Notified DSMC" and the "SAE Classification". If these have been entered and the email still has not been received, take a screen shot of the SAE in WISER and immediately email it out to all of the DSMC members listed in this SOP. In the subject line, indicate that this is a manual transmission of the SAE in lieu of the auto-generated email. It is required that a notification goes to the DSMC members immediately so that their assessment can be obtained within the 24 hour period requirement. Contact the Cancer Center Programmer/Analyst to alert that there is an issue with the auto-generated email.

The Clinical Members of DSMC to Notify by Phone or Page:

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Lesser	Hughes	Goodman	Reed	Porosnicu	Seegars	Lesser
Hughes	Goodman	Reed	Porosnicu	Seegars	Lesser	Hughes
Goodman	Reed	Porosnicu	Seegars	Lesser	Hughes	Goodman
Reed	Porosnicu	Seegars	Lesser	Hughes	Goodman	Reed
Porosnicu	Seegars	Lesser	Hughes	Goodman	Reed	Porosnicu
Seegars	Lesser	Hughes	Goodman	Reed	Porosnicu	Seegars

[redacted]

Definition of Unavailable:

As a general guideline if the first clinician that is contacted does not respond to the phone call or page within 30 minutes, then initiate contact with the next DSMC clinician listed in the table above on the particular day the SAE is being reported. Allow up to 30 minutes for the new DSMC clinician to respond to a phone call or page before contacting the next member in the table. These times (30 minutes) are a general guideline. Best judgment as a clinical research professional should be used giving considerations of the time of day, severity of the SAE, and other circumstances as to when it is appropriate to contact backup clinicians. If the event occurs near the end of day, then leave messages (voice or email) as appropriate and proceed with submitting the DSMC notification form. It is important to take reasonable steps and to document that some type of contact has been initiated to one or more of the clinical members of DSMC.

DSMC CLINICAN RESPONSIBILITY:

It is the responsibility of the DSMC clinician to review all reported events, evaluate the events as they are reported; and communicate a response to the Investigator, event reporter and the members of DSMC. The review will include but not be limited to the information reported; there may be times when additional information is needed in order for an assessment to be made and further communication directly with the investigator may be warranted. DSMC reserves the right to disagree with the Investigator's assessment. If DSMC does not agree with the Investigator, DSMC reserves the right to suspend the trial pending further investigation. If there is any immediate danger or harm that could be present for a future patient based on the information provided in the DSMC report then an immediate suspension of enrollment should be considered.

AMENDMENTS TO PREVIOUS REPORTS

If all pertinent information is unavailable with the initial submission, once the additional information is available **do not submit a new report**. Rather, go to the original email that was sent to the DSMC and using that email "reply to all". Entitle this new email "**Amendment** for (list date of event and patient ID)" this will avoid duplications of the same event. List the additional information being reported. This information needs to be entered into WISER as well. To do this, go to the Subject console and click SAEs on the left column. Click on the appropriate SAE number that needs updating. Then click Update. This will allow additional information to be added.

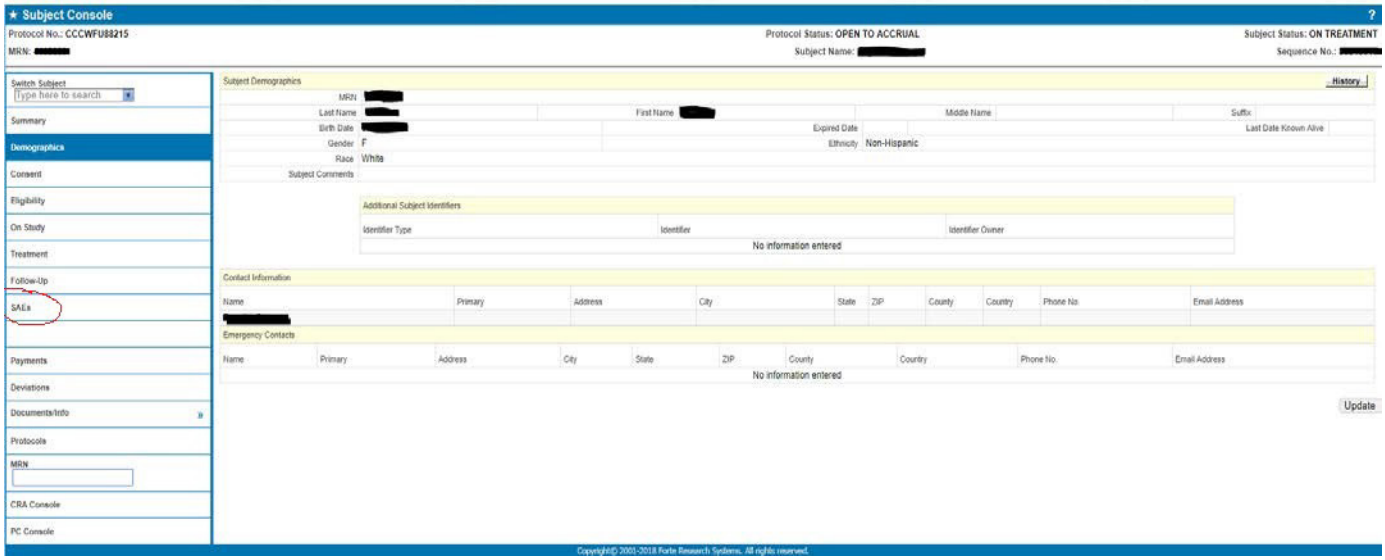
Acronyms

AE – Adverse Event
DSMC-Data and Safety Monitoring Committee
SAE-Serious Adverse Event
WFBCCC – Wake Forest Baptist Comprehensive Cancer Center
NCI-National Cancer Institute
WISER –Wake Integrated Solution for Enterprise Research

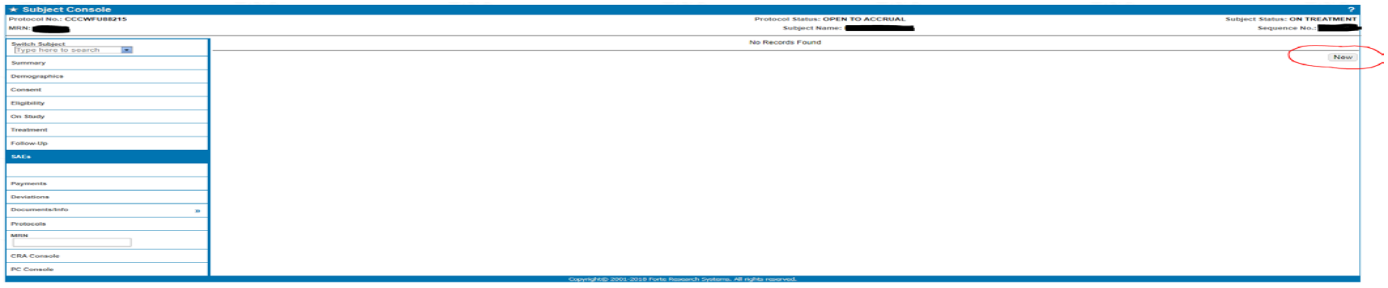
Screen Shots:

The following screen shots come from the SAE Console within the Subject Console in WISER.

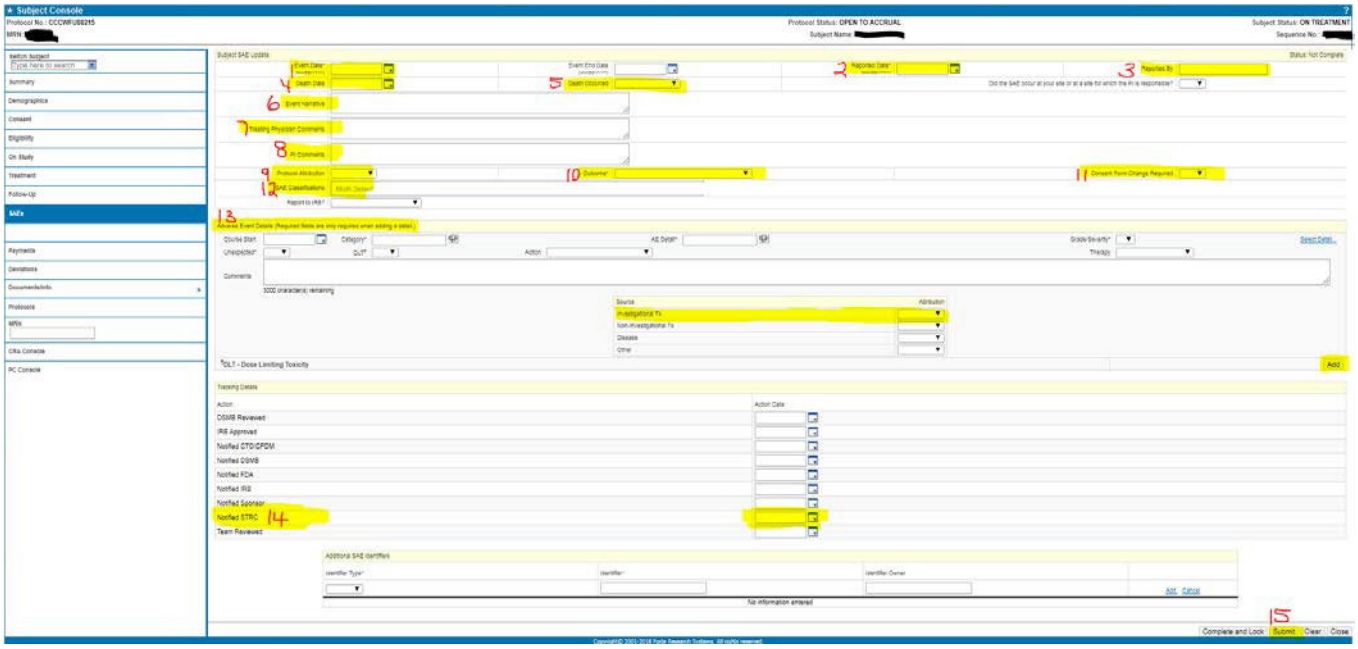
Screen Shot 1:



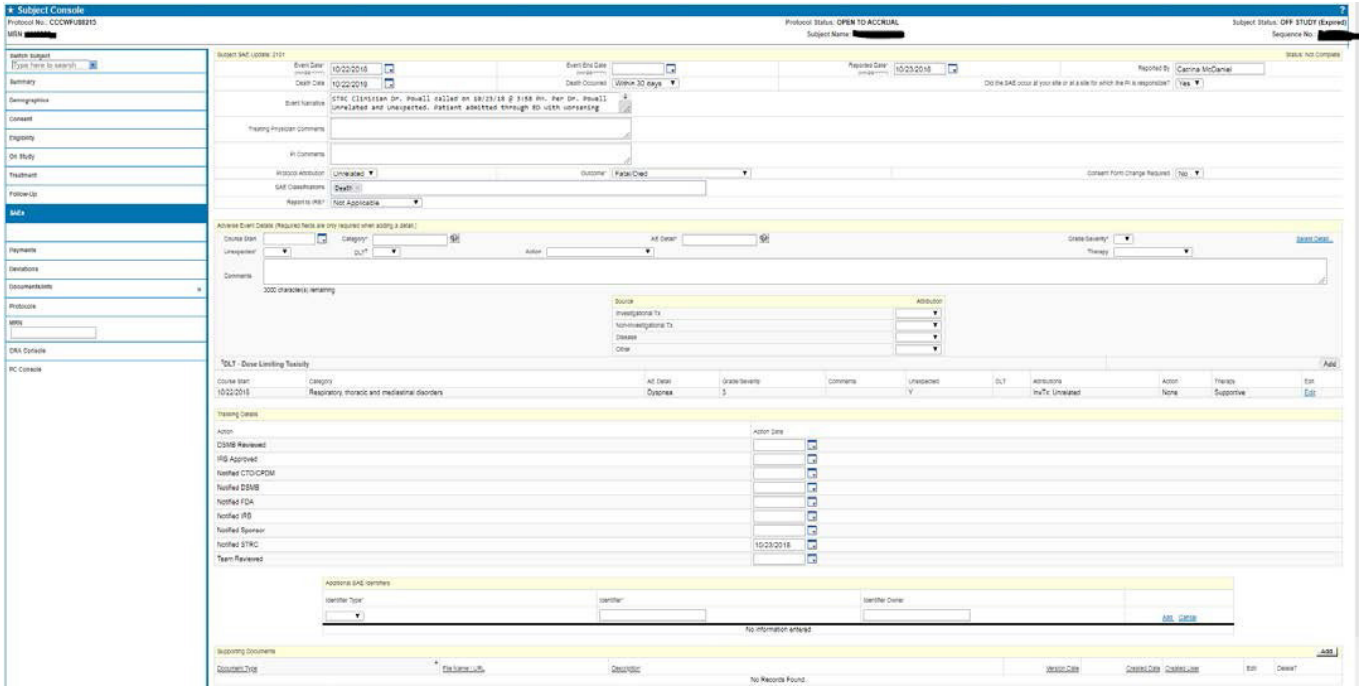
Screen Shot 2:



Screen Shot 3:



Screen Shot 4:



Appendix E – Adverse Event Log

WFBCCC Adverse Event (AE) Log

PI: _____ Subject PID: _____ **MRN: _____**

Cycle #: _____ **Cycle Start Date: _____** **Cycle Start Time: _____** **Cycle End Date: _____** **Cycle End Time: _____**

Adverse Event CTC Term	**Lab Value**	**Grade** (1-5) per CTC	**Start Date**	**End Date**	**Attribution** DEF=Definite PROB=Probable POSS=Possible UNLK=Unlikely UNRL=Unrelated	**Expected** N=No Y=Yes	**Serious Adverse Event Detail** NO=No LT=Life Threatening DTH=Death DIS=Disability HOS=Hospitalization CA=Caused congenital anomaly RI=Required intervention to prevent impairment	**Dose Limiting Toxitity (DLT)** N=No Y=Yes	**Action Taken** NO=None DR=Dose Reduced RI=Regimen Interrupted TD=Therapy discontinued INTR=Interrupted then reduced	**Therapy Given** NO=None SYM=Symptomatic SUP=Supportive VSUP=Vigorous supportive	**Reportable?** IRB-IRB STRC-STRC FDA-FDA SPON-Sponsor (Mark all that apply)	**Adverse Event Report (AER) Filed** N=No Y=Yes	**Outcome** R=Recovered TX=Still under treatment/ observation A=Alive with sequalae D=Died	**Treating MD Initials/Date**

Serious Adverse Event: Hospitalization; Disability; Birth Defect; Life-threatening; Death.

CTCAE Version 4 - http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

DSMC- Data and Safety Monitoring Committee — Version 1/10/18

Appendix F - Patient Drug Diary

Study Number: __ __ __ __ __ PID: ___ ___ ___ ___ ___ ___ ___ ___

Investigator: Roy Strowd, M.D. Date: __ __/__ __/__ __

Instructions: Complete the table below to track medication use.

Dose: **75 mg** ☐ **150 mg** ☐ **300 mg** ☐			Side effects (including unusual symptoms),
Date	**Day of one-week schedule**	**Taken**	
__ __/__ __/__ __	1	Yes ☐ No ☐	
__ __/__ __/__ __	2	Yes ☐ No ☐	
__ __/__ __/__ __	3	Yes ☐ No ☐	
__ __/__ __/__ __	4	Yes ☐ No ☐	
__ __/__ __/__ __	5	Yes ☐ No ☐	
__ __/__ __/__ __	6	Yes ☐ No ☐	
__ __/__ __/__ __	7	Yes ☐ No ☐	

Was the full 7 days completed? Yes ☐ No ☐

If No, was this due to side effects? Yes ☐ No ☐

Appendix G – Fixed Dosing Patient Drug Diary

Study Number: __ __ __ __ __ PID: ___ ___ ___ ___ ___ ___ ___ ___

Investigator: Roy Strowd, M.D. Date: __ __/__ __/__ __

Instructions: Complete the table below to track medication use.

Dose: 300 mg☐			
Date	**Day of six-week schedule**	**Taken**	Side effects (including unusual symptoms),
__ __/__ __/__ __	1	Yes ☐ No ☐	
__ __/__ __/__ __	2	Yes ☐ No ☐	
__ __/__ __/__ __	3	Yes ☐ No ☐	
__ __/__ __/__ __	4	Yes ☐ No ☐	
__ __/__ __/__ __	5	Yes ☐ No ☐	
__ __/__ __/__ __	6	Yes ☐ No ☐	
__ __/__ __/__ __	7	Yes ☐ No ☐	
__ __/__ __/__ __	8	Yes ☐ No ☐	
__ __/__ __/__ __	9	Yes ☐ No ☐	
__ __/__ __/__ __	10	Yes ☐ No ☐	
__ __/__ __/__ __	11	Yes ☐ No ☐	
__ __/__ __/__ __	12	Yes ☐ No ☐	
__ __/__ __/__ __	13	Yes ☐ No ☐	
__ __/__ __/__ __	14	Yes ☐ No ☐	
__ __/__ __/__ __	15	Yes ☐ No ☐	
__ __/__ __/__ __	16	Yes ☐ No ☐	
__ __/__ __/__ __	17	Yes ☐ No ☐	
__ __/__ __/__ __	18	Yes ☐ No ☐	
__ __/__ __/__ __	19	Yes ☐ No ☐	
__ __/__ __/__ __	20	Yes ☐ No ☐	
__ __/__ __/__ __	21	Yes ☐ No ☐	
__ __/__ __/__ __	22	Yes ☐ No ☐	
__ __/__ __/__ __	23	Yes ☐ No ☐	
__ __/__ __/__ __	24	Yes ☐ No ☐	
__ __/__ __/__ __	25	Yes ☐ No ☐	
__ __/__ __/__ __	26	Yes ☐ No ☐	
__ __/__ __/__ __	27	Yes ☐ No ☐	
__ __/__ __/__ __	28	Yes ☐ No ☐	

Dose: 300 mg☐			
Date	**Day of six-week schedule**	**Taken**	Side effects (including unusual symptoms),
__ __/__ __/__ __	29	Yes ☐ No ☐	
__ __/__ __/__ __	30	Yes ☐ No ☐	
__ __/__ __/__ __	31	Yes ☐ No ☐	
__ __/__ __/__ __	32	Yes ☐ No ☐	
__ __/__ __/__ __	33	Yes ☐ No ☐	
__ __/__ __/__ __	34	Yes ☐ No ☐	
__ __/__ __/__ __	35	Yes ☐ No ☐	
__ __/__ __/__ __	36	Yes ☐ No ☐	
__ __/__ __/__ __	37	Yes ☐ No ☐	
__ __/__ __/__ __	38	Yes ☐ No ☐	
__ __/__ __/__ __	39	Yes ☐ No ☐	
__ __/__ __/__ __	40	Yes ☐ No ☐	
__ __/__ __/__ __	41	Yes ☐ No ☐	
__ __/__ __/__ __	42	Yes ☐ No ☐	

Was the full six weeks completed? Yes ☐ No ☐

If No, was this due to side effects? Yes ☐ No ☐

Appendix H – Epworth Sleepiness Scale (ESS)

Study Number: __ __ __ __ __ PID: ___ ___ ___ ___ ___ ___ ___ ___

Investigator: Roy Strowd, M.D. Date: __ __/__ __/__ __

Epworth Sleepiness Scale

Name:_____Today's date: _____

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired?

This refers to your usual way of life in recent times.

Even if you haven't done some of these things recently try to work out how they would have affected you.

Use the following scale to choose the most appropriate number for each situation:

0 = would never doze
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing

It is important that you answer each question as best you can.

Situation	Chance of Dozing (0-3)
Sitting and reading	___
Watching TV	___
Sitting, inactive in a public place (e.g. a theatre or a meeting)	___
As a passenger in a car for an hour without a break	___
Lying down to rest in the afternoon when circumstances permit	___
Sitting and talking to someone	___
Sitting quietly after a lunch without alcohol	___
In a car, while stopped for a few minutes in the traffic	___

Appendix I – Pittsburgh Sleep Quality Index (PSQI)

Study Number: __ __ __ __ __ PID: ___ ___ ___ ___ ___ ___ ___ ___

Investigator: Roy Strowd, M.D. Date: __ __/__ __/__ __

The Pittsburgh Sleep Quality Index (PSQI) is an effective instrument used to measure the quality and patterns of sleep in adults. It differentiates "poor" from "good" sleep quality by measuring seven areas (components): subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction over the last month.

INSTRUCTIONS:
The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.
During the past month,

1. When have you usually gone to bed? _____

2. How long (in minutes) has it taken you to fall asleep each night? _____

3. What time have you usually gotten up in the morning? _____

4. A. How many hours of actual sleep did you get at night? _____

   B. How many hours were you in bed? _____

5. During the past month, how often have you had trouble sleeping because you	Not during the past month (0)	Less than once a week (1)	Once or twice a week (2)	Three or more times a week (3)
A. Cannot get to sleep within 30 minutes				
B. Wake up in the middle of the night or early morning				
C. Have to get up to use the bathroom				
D. Cannot breathe comfortably				
E. Cough or snore loudly				
F. Feel too cold				
G. Feel too hot				
H. Have bad dreams				
I. Have pain				
J. Other reason (s), please describe, including how often you have had trouble sleeping because of this reason (s):				
6. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?				
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?				
8. During the past month, how much of a problem has it been for you to keep up enthusiasm to get things done?				

9. During the past month, how would you rate your sleep qualityoverall?	Very good (0)	Fairly good (1)	Fairly bad (2)	Very bad (3)

SCORING

Component 1	#9 Score	C1 _____
Component 2	#2 Score (<15min (0), 16-30min (1), 31-60 min (2), >60min (3)) + #5a Score (if sum is equal 0=0; 1-2=1; 3-4=2; 5-6=3)	C2 _____
Component 3	#4 Score (>7(0), 6-7 (1), 5-6 (2), <5(3)	C3 _____
Component 4	(total # of hours asleep) / (total # of hours in bed) x 100 >85%=0, 75%-84%=!, 65%-74%=2, <65%=3	C4 _____
Component 5	# sum of scores 5b to 5j (0=0; 1-9=1; 10-18=2; 19-27=3)	C5 _____
Component 6	#6 Score	C6 _____
Component 7	#7 Score + #8 score (0=0; 1-2=1; 3-4=2; 5-6=3)	C7 _____

Add the seven component scores together _____

Global PSQI _____

Appendix J – Brief Fatigue Inventory (BFI)

Study Number: __ __ __ __ __ PID: ___ ___ ___ ___ ___ ___ ___ ___

Investigator: Roy Strowd, M.D. Date: __ __/__ __/__ __

Brief Fatigue Inventory

Throughout our lives, most of us have times when we feel very tired or fatigued. Have you felt unusually tired or fatigued in the last week? ☐ Yes ☐ No

1. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your fatigue right NOW.

0 1 2 3 4 5 6 7 8 9 10
No fatigue As bad as you can imagine

2. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your USUAL level of fatigue during past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No fatigue As bad as you can imagine

3. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No fatigue As bad as you can imagine

4. Circle the one number that describes how, during the past 24 hours, fatigue has interfered with your:

A. General activity
0 1 2 3 4 5 6 7 8 9 10
Does not interfere Completely interferes

B. Mood
0 1 2 3 4 5 6 7 8 9 10
Does not interfere Completely interferes

C. Walking ability
0 1 2 3 4 5 6 7 8 9 10
Does not interfere Completely interferes

D. Normal work (includes both work outside the home and daily chores)
0 1 2 3 4 5 6 7 8 9 10
Does not interfere Completely interferes

E. Relations with other people
0 1 2 3 4 5 6 7 8 9 10
Does not interfere Completely interferes

F. Enjoyment of life
0 1 2 3 4 5 6 7 8 9 10
Does not interfere Completely interferes

Appendix K – Cancer Fatigue Scale (CFS)

Study Number: __ __ __ __ __ PID: ___ ___ ___ ___ ___ ___ ___ ___

Investigator: Roy Strowd, M.D. Date: __ __/__ __/__ __

The Cancer Fatigue Scale

This questionnaire will ask you about any sense of fatigue you might be experiencing. For each ques- tion, please circle only one number you think most aptly describes your current state. Try to answer on the basis of first impressions, without thinking deeply about each question.

Right now . . .	No	A little	Somewhat	Considerably	Very much
1 Do you become tired easily?	1	2	3	4	5
2 Do you have the urge to lie down?	1	2	3	4	5
3 Do you feel exhausted?	1	2	3	4	5
4 Do you feel you have become careless?	1	2	3	4	5
5 Do you feel energetic?	1	2	3	4	5
6 Does your body felt heavy and tired?	1	2	3	4	5
7 Do you feel that you more often make errors while speaking?	1	2	3	4	5
8 Do you feel interest in anything?	1	2	3	4	5
9 Do you feel fed-up?	1	2	3	4	5
10 Do you feel you have become forgetful?	1	2	3	4	5
11 Can you concentrate on certain things?	1	2	3	4	5
12 Do you feel reluctant?	1	2	3	4	5
13 Do you feel that your thinking has become slower?	1	2	3	4	5
14 Can you encourage yourself to do anything?	1	2	3	4	5
15 Do you feel such fatigue that you don't know what to do with yourself?	1	2	3	4	5

The Calculation Method

Add the number together in every factor

Factor 1 = (items 1 + 2 + 3 + 6 + 9 + 12 + 15) − 7 P. (Physical subscale)

Factor 2 = 20 − (items 5 + 8 + 11 + 14) P. (Affective subscale)

Factor 3 = (items 4 + 7 + 10 + 13) − 4 P. (Cognitive subscale)

Add the factors together P. (Total scale score)

*Subtractions adjust for 0 as a state of no fatigue.

Appendix L – Beck Depression Inventory

The questionnaire consists of 21 groups of statements. After reading each group of statements carefully check the box next to the one statement in each group which best describes the way you have been feeling in **the past week, including today**. If several statements within a group seem to apply equally well, check each one. Be sure to read all the statements in each group before making your choices.

1. □ I do not feel sad.
   □ I feel sad.
   □ I am sad all the time and can't snap out of it.
   □ I am so sad or unhappy that I can't stand it.

2. □ I am not particularly discouraged about the future.
   □ I feel discouraged about the future.
   □ I feel I have nothing to look forward to.
   □ I feel that the future is hopeless and that things cannot improve.

3. □ I do not feel like a failure.
   □ I feel I have failed more than the average person.
   □ As I look back on my life, all I can see is a lot of failures.
   □ I feel I am a complete failure as a person.

4. □ I get as much satisfaction out of things as I used to.
   □ I don't enjoy things the way I used to.
   □ I don't get real satisfaction out of anything anymore.
   □ I am dissatisfied or bored with everything.

5. □ I don't feel particularly guilty.
   □ I feel guilty a good part of the time.
   □ I feel quite guilty most of the time.
   □ I feel guilty all of the time.

6. □ I don't feel I am being punished.
   □ I feel I may be punished.
   □ I expect to be punished.
   □ I feel I am being punished.

7. □ I don't feel disappointed in myself.
   □ I am disappointed in myself.
   □ I am disgusted with myself.
   □ I hate myself.

8. □ I don't feel I am any worse than anybody else.
   □ I am critical of myself for my weaknesses or mistakes.

□ I blame myself all the time for my faults.
□ I blame myself for everything bad that happens.

9. □ I don't have any thoughts of killing myself.
□ I have thoughts of killing myself, but I would not carry them out.
□ I would like to kill myself.
□ I would kill myself if I had the chance.

10. □ I don't cry any more than usual.
□ I cry more now than I used to.
□ I cry all the time now.
□ I used to be able to cry, but now I can't cry even though I want to.

11. □ I am no more irritated now than I ever am.
□ I get annoyed or irritated more easily than I used to.
□ I feel irritated all the time now.
□ I don't get irritated at all by the things that used to irritate me.

12. □ I have not lost interest in other people.
□ I am less interested in other people than I used to be.
□ I have lost most of my interest in other people.
□ I have lost all of my interest in other people.

13. □ I make decisions about as well as I ever could.
□ I put off making decisions more than I used to.
□ I have greater difficulty in making decisions than before.
□ I can't make decisions at all anymore.

14. □ I don't feel I look any worse than I used to.
□ I am worried that I am looking old or unattractive.
□ I feel that there are permanent changes in my appearance
□ I believe that I look ugly.

15. □ I can work about as well as before.
□ It takes an extra effort to get started at doing something.
□ I have to push myself very hard to do anything.
□ I can't do any work at all.

16. □ I can sleep as well as usual.
□ I don't sleep as well as I used to.
□ I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
□ I wake up several hours earlier than I used to and cannot get back to sleep.

17. □ I don't get more tired than usual.
□ I get tired more easily than I used to.

□ I get tired from doing almost anything.
□ I am too tired to do anything.

18. □ My appetite is no worse than usual.
□ My appetite is not as good as it used to be.
□ My appetite is much worse now.
□ I have no appetite at all anymore.

19. □ I haven't lost much weight, if any, lately.
□ I have lost more than 5 pounds.
□ I have lost more than 10 pounds.
□ I have lost more than 15 pounds.

I am purposefully trying to lose weight by eating less: □ Yes □ No

20. □ I am no more worried about my health than usual.
□ I am worried about physical problems like aches/pains, upset stomach, or constipation.
□ I am very worried about physical problems and it's hard to think of much else.
□ I am so worried about my physical problems that I cannot think about anything else.

21. □ I have not noticed any recent change in my interest in sex.
□ I am less interested in sex than I used to be.
□ I am much less interested in sex now.
□ I have lost interest in sex completely.

Appendix M – Neurocognitive Battery Record

Study Number: __ __ __ __ __ PID: ___ ___ ___ ___ ___ ___ ___ ___

Investigator: Roy Strowd, M.D. Date: __ __/__ __/__ __

Instructions: Complete the table below to track date of neurocognitive testing and assessments performed.

V1 Test Date:	Test Name:	Completed:	If not completed, state reason
__ __/__ __/__ __	Digit Span (DS)	Yes ☐ No ☐	
	Letter Number Sequencing (LNS)	Yes ☐ No ☐	
	Matrix Reasoning (MR)	Yes ☐ No ☐	
	Symbol Search (SS)	Yes ☐ No ☐	
	Coding (CD)	Yes ☐ No ☐	
	Controlled Oral Word Association Test (COWAT)	Yes ☐ No ☐	
	Trail Making Test Parts A and B (TMT A & B)	Yes ☐ No ☐	
	Montreal Cognitive Assessment (MoCA)	Yes ☐ No ☐	
	Total Score		

V3 Test Date:	Test Name:	Completed:	If not completed, state reason
__ __/__ __/__ __	Digit Span (DS)	Yes ☐ No ☐	
	Letter Number Sequencing (LNS)	Yes ☐ No ☐	
	Matrix Reasoning (MR)	Yes ☐ No ☐	
	Symbol Search (SS)	Yes ☐ No ☐	
	Coding (CD)	Yes ☐ No ☐	
	Controlled Oral Word Association Test (COWAT)	Yes ☐ No ☐	
	Trail Making Test Parts A and B (TMT A & B)	Yes ☐ No ☐	
	Montreal Cognitive Assessment (MoCA)	Yes ☐ No ☐	
	Total Score		

Appendix N – FACT Br (Version 4)

Study Number: __ __ __ __ __ PID: ___ ___ ___ ___ ___ ___ ___ ___

Investigator:, Roy Strowd, M.D. Date: __ __/__ __/__ __

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy.....	0	1	2	3	4
GP2	I have nausea.....	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family.....	0	1	2	3	4
GP4	I have pain.....	0	1	2	3	4
GP5	I am bothered by side effects of treatment.....	0	1	2	3	4
GP6	I feel ill.....	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home).....	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well.....	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun.....	0	1	2	3	4
GF7	I am content with the quality of my life right now.....	0	1	2	3	4

By circling one (1) number per line, please indicate how true each statement has been for you <u>during the past 7 days.</u>

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
Br1	I am able to concentrate.....	0	1	2	3	4
Br2	I have had seizures (convulsions).....	0	1	2	3	4
Br3	I can remember new things.....	0	1	2	3	4
Br4	I get frustrated that I cannot do things I used to.....	0	1	2	3	4
Br5	I am afraid of having a seizure (convulsion).....	0	1	2	3	4
Br6	I have trouble with my eyesight.....	0	1	2	3	4
Br7	I feel independent	0	1	2	3	4
NTX 6	I have trouble hearing	0	1	2	3	4
Br8	I am able to find the right word(s) to say what I mean.....	0	1	2	3	4
Br9	I have difficulty expressing my thoughts.....	0	1	2	3	4
Br10	I am bothered by the change in my personality.....	0	1	2	3	4
Br11	I am able to make decisions and take responsibility.....	0	1	2	3	4
Br12	I am bothered by the drop in my contribution to the family.....	0	1	2	3	4
Br13	I am able to put my thoughts together	0	1	2	3	4
Br14	I need help in caring for myself (bathing, dressing, eating, etc.).....	0	1	2	3	4
Br15	I am able to put my thoughts into action	0	1	2	3	4
Br16	I am able to read like I used to.....	0	1	2	3	4
Br17	I am able to write like I used to	0	1	2	3	4
Br18	I am able to drive a vehicle (my car, truck, etc.)	0	1	2	3	4
Br19	I have trouble feeling sensations in my arms, hands, or legs.....	0	1	2	3	4
Br20	I have weakness in my arms or legs	0	1	2	3	4
Br21	I have trouble with coordination.....	0	1	2	3	4
An 10						

I get headaches..... 0 1 2 3 4

Appendix O – Concurrent Medications Form

Study Number: ___ ___ ___ ___ ___ **PID:** ___ ___ ___ ___ ___ ___ ___ ___

PI: Roy Strowd, M.D._____ **Date (mm/dd/yyyy):** ___ ___/___ ___/___ ___ ___ ___

Instructions: Fill this form out at the baseline/pre-study visit and/or additional visits per protocol.

Study Visit (if needed per protocol):

- ☐ Baseline
- ☐ Visit 1
- ☐ Visit 2
- ☐ Visit 3
- ☐ Other visit: (please specify) _____

Current Medications List

Prescription Medications:

Name of Medication	Dose	Units	Frequency	Condition Medication Taken For	Start date (mm/dd/yy)	Stop date (mm/dd/yy)	Formulation	Route	Notes

Appendix P – Off-Study Form

Study Number: __ __ __ __ __	PID: ___ ___ ___ ___ ___ ___ ___ ___
Investigator:, Roy Strowd, M.D.	Date: __ __/__ __/__ __

Instructions: Complete this form if the patient either withdraws consent or is removed from the study.

Name of Person Competing form_____

Did the subject meet eligibility criteria for study enrollment? Yes ☐ No ☐

Was the subject removed from the study per physician decision? Yes ☐ No ☐
(if yes, move to #5)

Did the patient withdraw consent to participate in the study? Yes ☐ No ☐
(if yes move to #1)

Reason for patient withdrawal:

1. ☐ Unacceptable toxicity from solriamfetol
2. ☐ Did not want to participate anymore. Reason:
   _____
3. ☐Other: _____
4. Please specify what portion of the study the subject wishes to withdraw from:

   ☐ For just the solriamfetol administration only
   ☐ For all components of the research study (including follow up in the medical record)

Reason(s) for Removal:

5. ☐ Patient exhibited progression of disease
6. ☐ Unacceptable toxicity from solriamfetol
7. ☐ Investigator's discretion to withdraw patient from the study because continued participation in the study is not in the patient's best interest (*Describe below)
8. ☐ Undercurrent illness: a condition, injury, or disease unrelated to the intended disease for which the study is investigating, that renders continuing the treatment unsafe or regular follow-up impossible (*Describe below)
9. ☐ General or specific changes in the patient's condition that renders the patient ineligible for further investigational treatment (*Describe below)
10. ☐ Non-compliance with investigational treatment, protocol-required evaluations or follow-up visits (*Describe below)

11. ☐ Termination of the clinical trial by the clinical sponsor

Comment:

If reason for withdrawal includes #7, 8, 9, or 10 then please add comments clarifying this information)_____

_____

_____

_____

Appendix Q – MR Imaging Record

Study Number: __ __ __ __ __	PID: ___ ___ ___ ___ ___ ___ ___ ___
Investigator:, Roy Strowd, M.D.	Date: __ __/__ __/__ __

Instructions: Complete the table below to track date of MRI Brain throughout the study.

Date of Enrollment: __ __/__ __/__ __

Off Study Date: __ __/__ __/__ __

Please record the date of any MR imaging between the date of enrollment and off study dates. If there is no imaging in between these times, please record the date of the next MR imaging after the off study date. If there is no imaging available, please list the reason.

Date of neuroimaging	**Completed:**	**If not completed, state reason**
__ __/__ __/__ __	Yes ☐ No ☐	
__ __/__ __/__ __	Yes ☐ No ☐	
__ __/__ __/__ __	Yes ☐ No ☐	
__ __/__ __/__ __	Yes ☐ No ☐	
__ __/__ __/__ __	Yes ☐ No ☐	
__ __/__ __/__ __	Yes ☐ No ☐	
__ __/__ __/__ __	Yes ☐ No ☐	

Appendix R – Sleep Diary and Actigraphy Record

Week of ______	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Actigraph worn?	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No
Did you take a nap?	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No
How long did you nap?							
Time you fell asleep:	AM/PM						
Time you woke up:	AM/PM						
Did you take anything to help you sleep at night?	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No
If so, indicate amount:							
Prescribed medicine							
Over-the-counter							
Alcohol							
Time you entered bed?	AM/PM	AM/PM	AM/PM	AM/PM	AM/PM	AM/PM	AM/PM
Minutes/hours it took you to fall asleep?							
Number of times you awoke during the night?							
Time it took you to fall back asleep:							
First awakening	HR MIN	HR MIN	HR MIN	HR MIN	HR MIN	HR MIN	HR MIN
Second awakening	HR MIN	HR MIN	HR MIN	HR MIN	HR MIN	HR MIN	HR MIN
Third awakening	HR MIN	HR MIN	HR MIN	HR MIN	HR MIN	HR MIN	HR MIN
Fourth awakening	HR MIN	HR MIN	HR MIN	HR MIN	HR MIN	HR MIN	HR MIN
Fifth awakening	HR MIN	HR MIN	HR MIN	HR MIN	HR MIN	HR MIN	HR MIN
Sixth awakening	HR MIN	HR MIN	HR MIN	HR MIN	HR MIN	HR MIN	HR MIN
Indicate time you woke up:	AM/PM	AM/PM	AM/PM	AM/PM	AM/PM	AM/PM	AM/PM
Indicate time you got out of bed:	AM/PM	AM/PM	AM/PM	AM/PM	AM/PM	AM/PM	AM/PM
Falling asleep last night was:	□ Extremely difficult □ Difficult □ Fair □ Easy □ Very Easy	□ Extremely difficult □ Difficult □ Fair □ Easy □ Very Easy	□ Extremely difficult □ Difficult □ Fair □ Easy □ Very Easy	□ Extremely difficult □ Difficult □ Fair □ Easy □ Very Easy	□ Extremely difficult □ Difficult □ Fair □ Easy □ Very Easy	□ Extremely difficult □ Difficult □ Fair □ Easy □ Very Easy	□ Extremely difficult □ Difficult □ Fair □ Easy □ Very Easy
Staying asleep last night was:	□ Extremely difficult □ Difficult □ Fair □ Easy □ Very Easy	□ Extremely difficult □ Difficult □ Fair □ Easy □ Very Easy	□ Extremely difficult □ Difficult □ Fair □ Easy □ Very Easy	□ Extremely difficult □ Difficult □ Fair □ Easy □ Very Easy	□ Extremely difficult □ Difficult □ Fair □ Easy □ Very Easy	□ Extremely difficult □ Difficult □ Fair □ Easy □ Very Easy	□ Extremely difficult □ Difficult □ Fair □ Easy □ Very Easy
Rate the quality of sleep for this night:	□ Extremely difficult □ Difficult □ Fair □ Easy □ Very Easy	□ Extremely difficult □ Difficult □ Fair □ Easy □ Very Easy	□ Extremely difficult □ Difficult □ Fair □ Easy □ Very Easy	□ Extremely difficult □ Difficult □ Fair □ Easy □ Very Easy	□ Extremely difficult □ Difficult □ Fair □ Easy □ Very Easy	□ Extremely difficult □ Difficult □ Fair □ Easy □ Very Easy	□ Extremely difficult □ Difficult □ Fair □ Easy □ Very Easy
Rate your sleep this night compared to other nights:	□ Extremely difficult □ Difficult □ Fair	□ Extremely difficult □ Difficult □ Fair	□ Extremely difficult □ Difficult □ Fair	□ Extremely difficult □ Difficult □ Fair	□ Extremely difficult □ Difficult □ Fair	□ Extremely difficult □ Difficult □ Fair	□ Extremely difficult □ Difficult □ Fair

	□ Easy □ Very Easy	□ Easy □ Very Easy	□ Easy □ Very Easy	□ Easy □ Very Easy	□ Easy □ Very Easy	□ Easy □ Very Easy	□ Easy □ Very Easy

Appendix S – Glioma History

Study Number: __ __ __ __ __ PID: ___ ___ ___ ___ ___ ___ ___ ___

Investigator:, Roy Strowd, M.D. Date: __ __/__ __/__ __

Oncologic history

a) Glioma histologic diagnosis
   a. ☐ Astrocytoma
   b. ☐ Oligodendroglioma
   c. ☐ Glioblastoma
   d. ☐ Other: _____

b) WHO Grade of glioma: ☐ WHO Grade 2 ☐ WHO Grade 3 ☐ WHO Grade 4

c) Molecular data (e.g. IDH, MGMT, 1p19q)

Other Medical Conditions/Diagnoses (list all): _____

_____

_____

Molecular Features of the Primary Brain Tumor:

MGMT promoter methylation status	☐ Methylated ☐ Not methylated ☐ Not reported
IDH mutational status	☐ IDH1 mutated ☐ IDH2 mutated ☐ IDH1 and IDH2 wild type ☐ IDH1 and IDH2 testing not reported
1p/19q deletion status	☐ 1p19q codeleted ☐ 1p deletion only ☐ 19q deletion only ☐ 1p19q NOT codeleted (normal) ☐ 1p and 19q deletion not reported

Treatment Summary:

Treatment	Completed:	Date of Treatment(s)	Notes
Radiation	Yes ☐ No ☐		

Therapy		RT start date: __ __/__ __/__ __ RT end date: __ __/__ __/__ __	
Concurrent Chemotherapy	Yes ☐ No ☐	Name of chemotherapy: _____	
Adjuvant Chemotherapy	Yes ☐ No ☐	Name of chemotherapy: _____	

Recurrence Information:

Recurrence Number	**Recurrence (y/n):**	**Date of Recurrence**	**Treatment**
First Recurrence	Yes ☐ No ☐	__ __/__ __/__ __	
Second Recurrence	Yes ☐ No ☐	__ __/__ __/__ __	
Third Recurrence	Yes ☐ No ☐	__ __/__ __/__ __	
Fourth Recurrence	Yes ☐ No ☐	__ __/__ __/__ __	
Fifth Recurrence	Yes ☐ No ☐	__ __/__ __/__ __	

Appendix T – Telephone Script

Study Number: __ __ __ __ __	PID: ___ ___ ___ ___ ___ ___ ___ ___
Investigator:, Roy Strowd, M.D.	Date: __ __/__ __/__ __

Hello, my name is {TBD - Project Coordinator} and I am calling on behalf of {Wake Forest Baptist Medical Center}. May I please speak with {SUBJECT'S NAME}?

I am going to ask you several questions about any side effects that you have experienced in the last week. When answering these questions, I would like for you to think only about symptoms that you have had over the last 1 week. We will focus on the period of time that you have been on the current dose of the solriamfetol drug that is a part of this study.

Over the last 1 week, have you had any side effects from solriamfetol (the study drug)? ☐ Yes ☐ No

Over the last 1 week, have you had any of the following symptoms (and if so, please describe them)?

- ☐ Headache _____
- ☐ Nausea _____
- ☐ Decreased appetite _____
- ☐ Anxiety _____
- ☐ Diarrhea _____
- ☐ Dry mouth _____
- ☐ Insomnia _____
- ☐ Chest pain _____
- ☐ New shortness of breath _____
- ☐ Other _____