Randomized, double-blind trial of daridorexant to prevent delirium after heart surgery

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1. PURPOSE OF THE STUDY

Purpose: This feasibility study is designed to inform and ultimately support a grant application for funding for an adequately powered randomized, clinical trial (RCT) of daridorexant to prevent postoperative delirium. In this phase 2 study, we will test the following specific aims:

Aim 1: To demonstrate that we can recruit subjects for a placebo-controlled RCT of daridorexant to prevent postoperative delirium.
Target: We will enroll up to 16 subjects. Our recruitment goal is four subjects per month, for a total of 12 subjects completing the protocol.

Aim 2: To demonstrate that we can deliver study compounds to subjects per our proposed methods, including successful use of the OnCore Enterprise Clinical Trial Management System.
Target: All doses of study compound will be delivered successfully.

Aim 3: To demonstrate successful capture of preoperative, intraoperative, and postoperative data relevant for analyses during the conduct of this trial.
Target: We aim for 100% data capture, including subject retention through all doses of study compound.

Aim 4: To document all potential adverse events (AEs) and serious adverse events (SAEs).
Target: All subjects will be evaluated daily after receipt of study compound for AEs and SAEs.

2. BACKGROUND AND RATIONALE

A. Significance

A.1. Postoperative delirium is a serious, unmet public health need:

Delirium costs an estimated $38–$164 billion annually in the US and causes untold stress on patients, their families, and caregivers. It predicts greater risk of institutionalization, Alzheimer's disease and related dementias (ADRD), and death.[3-5] A third of all older adults have delirium during medical hospitalization. After cardiac surgery, 25–50% develop delirium.[6] More than 75% of critically ill adults and up to 85% of palliative care patients at the end of life develop delirium.[7] Despite its tremendous public health significance, most delirium is not preventable with current interventions,[8] and no intervention decisively improves delirium or its outcomes, including ADRD.[9] **There is a dire need for efficacious, well tolerated interventions to prevent and treat delirium.**

A.2. Delirium after heart surgery is especially important:

Cardiac surgery is plagued with delirium: rigorous studies report 25–50% incidence.[6] Post-cardiotomy delirium prevention has also often met with a sense of nihilism[10] due to unique challenges relative to other surgical cohorts,[11] only underscoring the need for efficacious delirium therapeutics in this population. **Post-cardiotomy delirium is associated with nearly 3x higher mortality, 6x higher risk of 24h+ mechanical ventilation, and longer ICU and hospital duration**.[12]

A.3. Sleep/wake disturbance (SWD) confer vulnerability to delirium[9,13-15]:

SWD is a core feature of delirium,[16-20] with research diagnostic criteria for delirium including SWD as one of delirium's three core domains.[20,21] Although whether SWD directly cause delirium has yet to be established,[22,23] there is strong evidence for the physiological link between SWD and delirium. Sleep is governed by the diencephalon (*i.e.*, hypothalamus and thalamus).[24] The anterior hypothalamus contains the sleep/wake "switch," which coordinates transitions between sleep and wake via dense reciprocal connections with all major sleep/wake centers in the brain.[25] The thalamus controls slow waves,[26] sleep spindles (linked with attentional disorders),[27] and sensory gating.[28] Each of these sleep/wake processes regulated by the diencephalon is disrupted in delirium,[29-32] strongly suggesting that maintaining or restoring sleep/wake integrity could combat delirium. Given that SWD are modifiable, they are an obvious and promising target for innovative pharmacological trials to prevent delirium.[9,13-15]

A.4. Prior "sleep" trials for delirium are methodologically limited[33]:

Most prior trials have studied *circadian* interventions and conflate the two related but dissociable processes of sleep/wake—process S (*sleep* propensity) and process C (endogenous *circadian* rhythm).[34] Melatonin/melatonin agonists influence circadian rhythms but have very limited effects on sleep quality.[35] Most prior circadian trials, which have yielded negative results,[36-47] have used *circadian* interventions with the goal of improving *sleep*, rather than studying them according to circadian principles, such as evaluating premorbid circadian phase to inform timing or evaluating circadian rhythmicity.[48] Sleep studies need to consider the specific effects of an intervention on sleep architecture (*e.g.*, REM sleep, N2 transients, N3), which is different from circadian studies that should evaluate effects on circadian rhythm (*e.g.*, 24-hr amplitude, dim-light melatonin onset).[49]

A.5. Orexin stabilizes sleep and wake states:

Orexin, also called hypocretin, is secreted by the tuberal hypothalamus and stabilizes sleep and wake states. Central orexin deficiency is the underlying cause of type 1 narcolepsy, which presents with excessive daytime sleepiness accompanied by either an irrepressible need to sleep or frank lapses into sleep.[50] The densest orexin projections are to the noradrenergic locus coeruleus with other projections to the cholinergic basal forebrain and serotonergic raphe nuclei.[50] **Orexin receptor (OX1R/OX2R) antagonism inhibits noradrenergic activity, thereby facilitating sleep onset**.[51] In humans, orexin antagonism increases total sleep time, reduces sleep latency, and reduces wake after sleep onset.[52]

A.6. Application of dual orexin receptor antagonists (DORAs) to neurodegenerative disorders:

Many reasons encourage studying DORAs in relation to delirium. DORAs (1) are efficacious in older adults;[52,53] (2) have good tolerability in older adults, including at the highest approved doses;[52,53] (3) do not suppress N2 transients, N3 sleep, or REM sleep;[54] (4) lack GABA-ergic activity;[55] (5) lack clinically significant anticholinergic effects;[56-58] (6) do not prolong the QTc to a clinically relevant degree;[56-58]; (7) have very limited abuse liability;[59] (8) do not cause rebound insomnia or withdrawal;[60] (9) improve total sleep time in obstructive sleep apnea;[60] (10) do not worsen obstructive sleep apnea at therapeutic doses;[61] (11) reduce stress-induced insomnia[62] and exert anxiolytic effects[63] in rodent models; and (12) appear to improve CSF clearance of Alzheimer disease biomarkers even after a single nightly dose.[64] Their effects on postural stability[65] and reaction time[66] are limited, and less than those of GABA-ergic agents like benzodiazepines. The three FDA-approved DORAs are similar pharmacologically; however, **daridorexant has the shortest half-life and negligible next-morning effects in clinical trials** (**Table 1**).[52,67,68] Given that cognitive performance is worst in the morning, especially attention[69] (*n.b.*, inattention is delirium's hallmark feature), and that delirium assessments often occur in the morning, the ideal DORA for delirium prevention should have negligible morning cognitive effects. Thus, daridorexant is the most promising DORA for delirium prevention.

Table 1 - Comparison of DORAs approved by the US FDA for insomnia			
	Daridorexant	**Suvorexant**	**Lemborexant**
OX1R binding affinity (Ki)	0.47 nM	0.55 nM	6.1 nM
OX2R binding affinity (Ki)	0.93 nM	0.35 nM	2.6 nM
Major metabolite	None	None	M10
Effects on QTc	Not clinically relevant	Not clinically relevant	Not clinically relevant
Mean T_{max}	1-2 hours	2 hours	1-3 hours
Volume of distribution	31 L	49 L	1970 L
Terminal $t_{1/2}$	8 hours	12 hours	17 hours
Metabolism	CYP3A4 (89%)	CYP3A > CYP2C19	CYP3A4 > CYP3A5
Severe liver impairment	"Not recommended"	"Not recommended"	"Not recommended"
Severe renal impairment	50% higher C_{max}	No dose adjustment	50% higher C_{max}

A.7. A new program of sleep-delirium trials:

This proposed trial is the first in an anticipated research program that aims to combat delirium with sleep interventions. **This project builds on the PI's K23 work investigating SWD in relation to delirium and will serve as a transition into translational research to develop sleep-focused delirium therapeutics.**

A.8. Whether sleep-focused interventions combat delirium, thus improving long-term cognitive outcomes, is unproven:

SWD are also closely associated with the permanent, progressive conditions of AD and CVD, which cause dementia, and considered a potential mechanism causing or accelerating these conditions,[14,70-73] perhaps by way of disrupted glymphatic clearance.[74] If (a) delirium mediates the relationship between SWD and AD/CVD and (b) preserving healthy sleep/wake prevents delirium,[64,75-77] then preventing delirium could prevent subsequent AD/CVD.[73] **What the field needs are conclusive data linking discrete sleep/wake interventions with the prevention of delirium and its dire cognitive and functional outcomes, including ADRD.** This project is aligned with the ADRD Milestones as it investigates targets of delirium vulnerability along with longer-term outcomes[9] by examining the mechanisms that link delirium physiology with its sequelae.[78]

A.9. Summary of significance:

Although delirium is an acute event, it often has permanent effects on patients' cognition and function. **To date, no medication is FDA-approved to prevent or treat delirium, along with its terrible costs to patients, their families, and health systems.**

B. Innovation

B.1. The orexin system invites delirium-related investigation:

Orexin is a promising alternative target to GABA for sleep pharmacology, especially in older adults. Early evidence suggests that DORAs may have a role in relation to delirium.[75,76,79-83] Both published RCTs of the DORA suvorexant to prevent delirium were positive but have methodological limitations, including that neither was double-blind. The first, from 2017, randomized 72 ICU and medical unit patients (mean age 78) to suvorexant or placebo in a "rater blind" manner and found a lower delirium incidence with suvorexant: 0 (0%) vs 6 (17%), $p = 0.025$.[75] The second, from 2018, randomized ICU patients to placebo or standard care and found a longer time to delirium with suvorexant (6.3d vs 5.7d, log–rank test $p < 0.05$);[84] however, 80% of comparison arm subjects arm received as-needed trazodone 25 mg qhs, confounding

clinical interpretation. Critical readers are skeptical about these data, as with any delirium study that finds a 0% delirium incidence in any study arm. Further, rigorous delirium trials have often failed to replicate early delirium studies: for instance, despite a promising 2014 ramelteon trial[85] (*n.b.*, from the authors of the 2017 suvorexant trial above) have not held up, as shown in a 2023 meta-analysis.[86] Moreover, compelling data will be needed to overcome a general apprehension re the use of sleep aids in older adults and the prevailing convention that they be used only as a "last resort."[87] **The field awaits the first double-blind RCT to prevent postop delirium and the first delirium prevention RCT of daridorexant.**

B.2. This study employs methodologically rigorous trial design using a true sleep aid:

As above, most prior "sleep" studies for delirium have investigated circadian interventions rather than interventions that improve sleep quality. This study aims to overcome the limitations of these prior trials by using an agent demonstrated to improve sleep quality and shorten wake bout duration using rigorous trial design (**Error! Reference source not found.**).

Table 2 - Considerations in sleep-delirium trials

Methodological consideration	**Limitations of prior trials**
The agent should enhance sleep.	Agents that entrain circadian phase.
The sleep aid should be taken *each* night before delirium assessments.	Several trials with non-nightly dosing.[39,40,42,46,47]
Sleep should be evaluated across subjects as a measure of primary effect	Most have neglected to assess sleep.[39-41,43,44,47]
Baseline sleep health should be evaluated.	Very rare in prior studies (*e.g.*[46]).
Accounting for in-hospital sleep disruptions.	Done in only three (*i.e.*, [36,37,45]).
Measure of ADRD biomarkers	Not done previously.

B.3. This project represents a transition from observational to interventional research for the PI:

This trial represents the first of an anticipated program of sleep-focused clinical trials to prevent as well as treat delirium. The delirium field is replete with observational research in delirium predictors and outcomes.[88,89] However, there is far less translational inquiry, and precious little evidence of efficacious interventions.[90] **A new generation of double-blind, placebo-controlled trials is urgently needed in the delirium field.**

B.4. Summary of innovation:

This daridorexant trial studies a highly promising, novel intervention to prevent postop delirium in older adults, a condition for which there is no approved medication and little translational inquiry. Preventing delirium would improve postop recovery and well-being and might even reduce the neuropathological progression of AD. **This is the first trial to study daridorexant to prevent delirium in any context.** Establishing that daridorexant prevents delirium could have immediate, transformative value for clinical practice.

3. ADMINISTRATIVE ORGANIZATION

This single-site trial represents a collaboration among the Department of Psychiatry, Department of Anesthesiology, and the Department of Surgery, Division of Cardiac Surgery. Randomization with a block size of six and drug dispensing will occur through Investigational Drug Services (IDS) at Strong Memorial Hospital (SMH). Prospective subjects may be identified in the hospital while awaiting surgery, at the time of outpatient evaluation by a cardiac surgeon, or in conjunction with anesthesiology during pre-surgical history and physical, typically performed at the Center for Perioperative Medicine.

4. STUDY DESIGN

This double-blind, parallel-group trial will randomize patients having cardiac surgery—either surgical aortic valve replacement (SAVR) or coronary artery bypass graft (CABG) surgery—to oral daridorexant 50 mg or identical-appearing placebo. The primary outcomes are feasibility and safety. Study subjects will provide written informed consent after receiving a complete description of the study. See **Figure 1** below for a timeline of study assessments (not to scale).

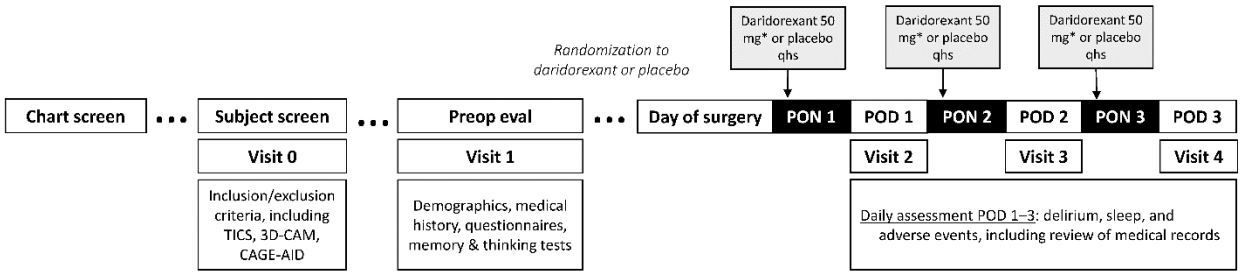

Figure 1 – Timeline of Study Assessments

Abbreviations: **3D-CAM**, 3-minute Diagnostic interview for the Confusion Assessment Method; **CAGE-AID**, CAGE [an acronym for "Cut down, Annoyed, Guilty, Eye-opener"] Adapted to Include Drugs; **POD**, postoperative day; **PON**, postoperative night; **TICS**, Telephone Interview for Cognitive Status
*25 mg for subjects on a moderate 3A4 inhibitor (see 4.2 STUDY INTERVENTION below for details)

4.1 SUBJECT POPULATION

We will enroll 16 persons scheduled to have SAVR or CABG at SMH, with the goal of having 12 subjects complete the protocol.

Choice of study population:

We propose a cardiac surgery cohort for several reasons. (1) Surgery provides a convenient model for understanding delirium pathophysiology and interventions as it allows for describing the sample at baseline and prospectively evaluating a cohort at elevated risk of delirium. (2) Cardiac surgery is associated with a 25–50% delirium incidence[6], due in large part to the older mean age of this population. As noted above, we have found 30% delirium incidence after SAVR at our institution. (3) We select a cardiac surgery cohort over a hip repair cohort as the pain associated with hip pathology and the postop surgical site affects sleep positions before and after surgery, which contributes to SWD, thereby introducing a potential confound.

The subjects in this trial do not qualify as vulnerable populations.

4.2 STUDY INTERVENTION

We will administer enteral daridorexant 50 mg each evening before bedtime, from 8 to 10 PM. Per the package insert,[58] subjects taking a moderate inhibitor of CYP 3A4 (per searchable FDA site[92]) will receive a reduced dose of 25 mg. Moderate inhibitors of 3A4 include: aprepitant, ciprofloxacin, conivaptan, crizotinib, diltiazem, dronedarone, erythromycin, fluconazole, grapefruit juice, imatinib, isavuconazole, verapamil. Of these, those most likely to be present are the antibacterials ciprofloxacin or erythromycin or the calcium channel blockers diltiazem or verapamil.

Choice of agent and dose:

DORAs represent a promising class of agents for delirium studies. In a phase 3 trial vs placebo, daridorexant 50 mg reduced wake after sleep onset (WASO) and latency to persistent sleep (LPS) on polysomnography (-22.8 min [95% CI -28.0 to -17.6); -11.4 min [-16.0 to -6.7], respectively), as well as

improved self-reported total sleep time (TST) (22.1 min [14.4 to 29.7]) and Insomnia Daytime Symptoms and Impacts Questionnaire sleepiness scores (-1.8 [-2.5 to -1.0).[52] Lower doses (10 & 25 mg) had less effect on sleep outcomes, with some not reaching statistical significance.[52] Although the 50-mg dose had greater efficacy, its AEs were nearly identical to that of lower doses (**Table 3**, see below[52]). Daridorexant improved WASO, LPS, and subjective TST comparably in older (≥ 65 yr) and younger adults (< 65 yr), with nearly identical rates of AE.[53] Another concern for most sleep aids is risk of falls; however, among older adults, **falls were numerically *less likely* with either 25 or 50 mg daridorexant than with placebo (1/119 [0.8%], 1/119 [0.8%], 4/122 [3.3%], respectively)**.[53] Daridorexant improves not only sleep but also next-day functioning, as one would hope for an ideal sleep aid. Given that central orexin deficiency is the putative cause of type 1 narcolepsy, core features of narcolepsy are theoretically possible with DORAs. Nevertheless, among older adults, these were extremely rare: 1/121 taking 25 mg daridorexant reported excessive daytime sleepiness, and 1/119 (1%) on daridorexant 50 mg reported sleep paralysis.[53] **We propose using 50 mg rather than 25 mg to maximize the chances of clinical effect, as this higher dose does not appear to increase the risk of AEs**.

Table 3 - Adverse events (AEs) & serious AEs (SAEs) with daridorexant (DAR) & placebo[52]

	Placebo Study 1 n=309	Placebo Study 2 n=306	**DAR 50 mg Study 1 n=310**	DAR 25 mg Study 2 n=308	DAR 25 mg Study 2 n=308	DAR 10 mg Study 2 n=306
Any AE	105 (34%)	100 (33%)	**116 (38%)**	117 (38%)	121 (39%)	117 (38%)
Any SAE	7 (2%)	7 (2%)	**3 (1%)**	2 (1%)	3 (1%)	3 (1%)
Nasopharyngitis	20 (6%)	16 (5%)	**20 (6%)**	21 (7%)	13 (4%)	16 (5%)
Headache	12 (4%)	11 (4%)	**19 (6%)**	16 (5%)	15 (5%)	12 (4%)
Somnolence	6 (2%)	4 (1%)	**5 (2%)**	11 (4%)	10 (3%)	6 (2%)

Choice of dosing days/times:

We will give 50 mg daridorexant (25 mg to those on moderate 3A4 inhibitor, as above) or placebo 8-10 PM on the first 3 postop nights and evaluate delirium on each of the days following administration—*i.e.*, POD 1–3. We give study agent the night prior to each day's assessment because **the prior night's sleep directly impacts cognition the next day**. Sleep restriction causes neurocognitive impairment the following day with the most pronounced effects in sustained attention (vigilance).[93] We choose 8-10 PM because daridorexant's T_{max} is 1–2 hr. This (1) allows time for its soporific effect and (2) is early enough to mitigate next-morning sedation).[52,67,68] For any subject still intubated during the 8-10 PM window, we will allow for administration up to midnight in the event that they are extubated prior to midnight. This is to maximize the likelihood of administration on the first postoperative night.

Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or subject populations are changed:

On September 18, 2024, we received a determination from the US FDA that our proposed trial "meets all meets all of the requirements for exemption from the IND regulations and, therefore, an IND is not required to conduct [this] investigation." See attached document, "FDA exemption determination (24-09-18)."

Medication and matching placebo will be stored by IDS, who will be responsible for randomization subjects to study arms, keeping records on medication storage, and ensuring timely dispensing.

5. INCLUSION

Inclusion criteria:

≥ 60 yrs; having cardiac surgery at Strong Memorial Hospital; can provide consent; able to speak, read, and write English (as the instruments, including semi-structured interviews, used in this protocol have been validated in English); family member or close friend for collateral.

Exclusion criteria:

Exclusion criteria with rationales are described in **Table 4**. Subjects will be screened in person or by phone for eligibility.

Table 4 - Exclusion criteria with explanation

Exclusion criteria	**Definition** (*rationale*)
Prior cardiotomy	Per self-report or chart (*sequelae of prior surgery)*
Infectious endocarditis	Per chart (*potential septic emboli*)
Emergency surgery	Per chart (*baseline eval impossible*)
Delirium at baseline	Positive 3D-CAM (*limit to incident delirium*)
Auditory/visual impairment prevents study procedures	Per self-report or demonstrated inability during baseline visit (*inability to participate*)
Alcohol/substance misuse	CAGE-AID score of 2 or greater (*exclude cognitive effects of substances*)
Psychotic disorder	Per self-report or chart (*can confound delirium assessment*)
Dementia-level deficits	Per self-report, chart, or TICS < 27 (*exclude effects of dementia on delirium assessments*)
Use of a sleep aid	Any prescribed sleep aid being taken at least every other night (*potential confound*)
Use of a strong 3A4 inhibitor (per FDA website[92])	Ceritinib, clarithromycin, cobicistat, idelalisib, itraconazole, ketoconazole, nefazodone, nelfinavir, posaconazole, ritonavir, telithromycin, voriconazole (*increases drug exposure*)
Intolerance to daridorexant	Per self-report or chart (*safety*)
Severe kidney or liver impairment	Child-Pugh score ≥ 7, Cockcroft-Gault < 30 mL/min, or current dialysis (*safety*)
Narcolepsy	Per self-report or chart (*daridorexant is contraindicated in narcolepsy*)
Prior suicide attempt	Per self-report or chart (*package insert indicates a risk of worsening depression or suicidality*)
Suicidal ideation at baseline assessment	Per self-report (*package insert indicates a risk of worsening depression or suicidality*)
Any condition that in the opinion of the PI compromises patient safety or data quality if enrolled in the study	

6. RECRUITMENT METHODS

Study personnel, including the principal investigator and research coordinator, who have routine access to the cardiac surgery clinic and operating room schedules, will pre-screen patients scheduled for SAVR or CABG in direct collaboration with cardiac surgeons and anesthesiology team. A member of the surgery or anesthesiology team will refer eligible study candidates to study personnel (see Referral form). Referred patients will be contacted by study personnel either in person during a scheduled clinic visits or by phone, as feasible.

7. CONSENT PROCESS

Verbal consent:

When contacting study referrals, study personnel will obtain verbal consent to complete a 10-minute assessment to assess study eligibility and document this by signing and keeping on file a copy of the Recruitment Script for that study referral. To confirm eligibility, we will review inclusion and exclusion criteria and screen patients using the Telephone Interview for Cognitive Status (TICS)[94] and CAGE-Adapted to Include Drugs (CAGE-AID).[95] As this work ultimately aims to identify an intervention to prevent cognitive impairment, we exclude dementia by chart review (prior diagnosis) and by phone (self-reported diagnosis or TICS < 27 [equivalent to MMSE < 24]). We include mild cognitive impairment (MCI) to increase the likelihood of postoperative delirium occurring in our sample.[96] These decisions balance the need for homogeneity *vs* generalizability of our sample.

Signed consent:

Prior to conducting any study procedures, subjects will complete the full informed consent process with research personnel. Research staff will first describe the study to eligible subjects and review the informed consent document. Subjects will then be given as much time to read the consent document as they wish and to ask any questions or discuss any aspect of the study. The subject will be invited to sign the written informed consent form, which will also be signed by research personnel obtaining consent (one copy will be given to the subject and the other copy will be kept under double locked conditions). The consent form includes contact information for study personnel.

Potential subjects for this study will be presumed to have capacity, especially as they have just recently provided consent for anesthesia and heart surgery. However, if the PI has any concerns over whether the subject has the capacity to participate when discussing the study protocol and reviewing what will be required of the subject in this study he will assess capacity. If other trained research personnel are enrolling the subject and has any concerns, he or she will contact the PI (a psychiatrist) who will personally conduct a clinical assessment of decision-making capacity (*i.e.*, communicate a decision of whether to join the study, comprehending the study's purpose, procedures, and potential risks/benefits, appreciate the study's potential impact on recovery, and the ability to make a reasoned decision), either in person or by phone. Patients who lack capacity to consent to study procedures will be excluded from this study, which will limit variance in baseline cognition.

Study partner:

This study protocol requires that subjects have a reliable informant to allow for assessment of cognitive status at baseline. We complete the semi-structured Clinical Dementia Rating (CDR) items with the study partner to ensure we have a good understanding of the subject's memory, problem solving ability, and daily activity. Our conversations with study partners usually take 10–15 minutes and can be either in person or by phone. If the subject develops delirium, their study partner or someone else who is a legally authorized representative will help them decide regarding continued study participation.

Requested Waiver of Documentation for Verbal Consent Process

https://www.rochester.edu/ohsp/documents/ohsp/pdf/policiesAndGuidance/Policy_701_Informed_Consent.pdf

To establish study eligibility, we will be conducting a 10-minute cognitive screen—the Telephone Interview for Cognitive Status (TICS). This will be performed prior to obtaining written consent and enrollment into the study. We will not be recording any personally identifiable information as part of this assessment. We will keep the screening results of individuals screened for eligibility, including TICS results, so we can characterize the broader sample of those referred for study participation. This will also allow us to compare the set of referred individuals who were found to be study ineligible vs study eligible,

which will inform future research in this clinical population. The potential study subject is providing verbal consent for screening, and the brief screen would satisfy criterion 9.1.2 under RSRB policy 701 as "the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context [45 CFR 46.117(c) and 21 CFR 56.109(c)].

8. STUDY PROCEDURES

See **Table 5** below for the Schedule of Activities

Table 5 - Schedule of activities

Assessment	**Screening** (15 min)	**Baseline** (1 hr)	**PON 1–3** (with bedtime meds)	**POD 1–3** (15 min)	**POD 3–7** (15 min)
Verbal consent	X				
CAGE-AID	X				
Written consent		X			
Demographics		X			
CCI		X			
Medication list		X			
Cognition/function					
TICS	X				
MoCA		Full, v8.1			
Lawton		X			
CDR		X			
WTAR		X			
Delirium					
3D-CAM	X			X	X†
DRS-R98				X	X†
Mental health					
PHQ-9		X			
GAD-7		X			
Sleep-related					
PSQI		X			
ESS		X			
RCSQ				X	X†
Medication administration			X		
AEs/SAEs					
Questionnaire		X		X	
Chart review*				X	X†
Subject to guess whether they received daridorexant or placebo				POD 3	

Abbreviations: **3D-CAM**, 3-Minute Diagnostic Interview for Confusion Assessment Method; **CAGE-AID**, CAGE [acronym for "Cut-down, Annoyed, Guilt, Eye-opener"] adapted to include drugs; **CCI**, Charlson comorbidity index; **CDR**, Clinical Dementia Rating; **DISH**, Depression Interview and Structured Hamilton; **DRS-R98**, Delirium Rating Scale, Revised 98; **ESS**, Epworth Sleepiness Scale; **GAD-7**, 7-item Generalized Anxiety Disorder scale; **Lawton**, Lawton Instrumental Activities of Daily Living; **MoCA**, Montreal Cognitive Assessment; **PHQ-9**, 9-item Patient Health Questionnaire; **POD**, postoperative day; **PON**, postoperative night (*i.e*, the night of POD 0 [the day of surgery] is defined as PON 1); **PSQI**, Pittsburgh Sleep Quality Index; **RCSQ**, Richards-Campbell Sleep Questionnaire; **TICS**, Telephone Interview for Cognitive Status; **WTAR**, Wechsler Test of Adult Reading

*For evidence of adverse events, documentation of delirium, potential sleep confounds

†Daily assessments for delirium and sleep will continue if the subject is delirious on POD 3, until delirium resolves.

Screening procedures:

As indicated under **7. CONSENT PROCESS** above, consent will involve two steps—a verbal consent for study eligibility screening and, subsequently, signed consent. When obtaining verbal consent, we will

indicate to study prospects that the eligibility questions take 5–10 minutes. We indicate that we keep responses to screening questions, even for those who don't end up taking part, so, as a result and explain that we do not record personally identifying information during the screening process. Before proceeding with the remainder of the eligibility assessment, we also ask the prospective subject to affirm the availability of a study partner should they participate in the study.

Study duration:

Study subjects will participate from the initial screening evaluation prior to surgery, which is usually 1–2 weeks prior to scheduled surgery, through the third postoperative day after surgery (*note*: as in the following paragraph, assessments may be continued past POD 3 if the subject is found to have delirium on POD 3). Most subjects, then, will be enrolled in the study for roughly 2 weeks. However, the duration of study participation will be dependent on the scheduling of preoperative anesthesiology visit in relation to date of surgery.

Choice of POD and assessments for delirium:

We assess delirium on POD 1–3 with the DRS-R-98 as validated based on clinical interview under the supervision of a psychiatrist.[99] We omit delirium assessment on POD 0 because (1) patients are intubated and sedated until the evening of POD 0 and (2) to exclude emergence delirium (*n.b.*, a distinct physiological event due to anesthetic effects[100]). With one exception (see below), we restrict delirium assessments to POD 3 because (1) patients are often discharged on POD 3 or 4, (2) postop delirium peaks on POD 2 and 3, coincident with the peak of postop inflammation,[101,102] and (3) this allows a commensurate 3-day period across subjects to evaluate for delirium during the days of greatest risk. We use DRS-R-98 as it is well validated and the most robust tool for characterizing delirium phenomenology.[1,16,17,20,21,103] Regarding the exception referenced above: to determine delirium duration in all subjects, we continue to perform daily delirium assessments for any subject positive for delirium on POD 3 until no longer positive. Regardless of whether delirium assessments continue beyond POD 3, subjects will still receive study drug for only the first three nights after surgery.

Number of visits:

Subjects will have four (or up to a maximum of 8, if a person continues to score positive for delirium on POD 3 through POD 6) in-person visits with study personnel (see **Figure 1**, Timeline of Study Assessments in Section 4. STUDY DESIGN).

Blinding, including justification:

Blinding of study staff, clinical staff, and the patient is critical for this trial, which test whether daridorexant prevents postoperative delirium.

Justification of why subjects will not receive routine care or will have current therapy stopped:

Subjects will receive routine surgical and postoperative care. This trial adds exposure only to daridorexant or placebo to test whether daridorexant prevents delirium. No current therapy will be stopped or modified.

Justification for inclusion of a placebo group:

The use of a placebo treatment is essential to understand the effects (both positive and negative) of daridorexant exposure. Placebo comparison is the only way that we can understand what is likely due to daridorexant and what is not.

9. RISKS

Medical risks, listing all procedures, their major and minor risks and expected frequency

Below, **Table 6** lists the most common risks of daridorexant based on two pre-marketing studies.

Table 6 - Adverse events (AEs) and serious adverse events (SAEs) with daridorexant (DAR) and placebo[52]

	Placebo Study 1 n=309	Placebo Study 2 n=306	**DAR 50 mg Study 1 n=310**	DAR 25 mg Study 2 n=308	DAR 25 mg Study 2 n=308	DAR 10 mg Study 2 n=306
Any AE	105 (34%)	100 (33%)	**116 (38%)**	117 (38%)	121 (39%)	117 (38%)
Any SAE	7 (2%)	7 (2%)	**3 (1%)**	2 (1%)	3 (1%)	3 (1%)
Nasopharyngitis	20 (6%)	16 (5%)	**20 (6%)**	21 (7%)	13 (4%)	16 (5%)
Headache	12 (4%)	11 (4%)	**19 (6%)**	16 (5%)	15 (5%)	12 (4%)
Somnolence	6 (2%)	4 (1%)	**5 (2%)**	11 (4%)	10 (3%)	6 (2%)

The following three images are taken from the daridorexant package insert:

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in practice.

The safety of QUVIVIQ was evaluated in three placebo-controlled clinical studies (two 3-month studies of identical design [Study 1 and Study 2], and a 9-month extension study [Study 3]). Study 1 evaluated 50 mg and 25 mg doses of QUVIVIQ, while Study 2 evaluated a 25 mg dose and a 10 mg dose of QUVIVIQ. The 10 mg dose is not an approved dose. A total of 1232 patients (including approximately 40% elderly patients [≥ 65 years old]), received QUVIVIQ 50 mg (N = 308); 25 mg (N = 618); or 10 mg (an unapproved dose) (N = 306). A total of 576 patients were treated with QUVIVIQ for at least 6 months and 331 for at least 12 months.

Most Common Adverse Reactions

The most common reported adverse reaction (in at least 5% of patients and greater than placebo) during double-blind treatment in Study 1 was headache.

Table 1 shows adverse reactions that occurred in at least 2% of patients treated with QUVIVIQ and more frequently than in patients who received placebo in Study 1.

Table 1 Adverse Reactions Reported in ≥ 2% of QUVIVIQ-treated Patients and Greater than in Placebo-treated Patients in a 3-Month Placebo-Controlled Study (Study 1)

	QUVIVIQ 25 mg (N=310) %	QUVIVIQ 50 mg (N=308) %	Placebo (N=309) %
Nervous System Disorders			
Headache*	6	7	5
Somnolence or fatigue*	6	5	4
Dizziness*	2	3	2
Gastro-intestinal disorders			
Nausea*	0	3	2

* The following terms were combined:
Headache includes: headache, tension headache, migraine, migraine with aura, head discomfort
Somnolence or fatigue includes: somnolence, sedation, fatigue, hypersomnia, lethargy
Dizziness includes: dizziness, vertigo, labyrinthitis
Nausea includes: nausea, vomiting, procedural nausea

Other Adverse Reactions Observed During Clinical Trials (Study 1 and Study 2)

Other adverse reactions of < 2% frequency but greater than placebo are shown below. The following do not include adverse reactions 1) for which a drug cause was remote, 2) that were so general as to be uninformative, or 3) that were not considered to have clinically significant implications.

- Sleep paralysis was reported in 0.5% and 0.3% of patients receiving QUVIVIQ 25 mg and 50 mg, respectively, compared to no reports for placebo.
- Hypnagogic and hypnopompic hallucinations were reported in 0.6% of patients receiving QUVIVIQ 25 mg compared to no cases with QUVIVIQ 50 mg or placebo.

6.2 Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of QUVIVIQ. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Psychiatric disorders: Nightmares or abnormal dreams

Immune system disorders: Hypersensitivity (including angioedema, rash, urticaria)

Safety assessments:

In this trial, we obtain demographics and baseline assessment of medical morbidity, medications, cognitive status, and self-report sleep & mental health. Obtaining such information does not entail significant foreseeable risk beyond limited risk of psychological distress or questionnaire fatigue. As we will be completing the 9-question Patient Healthcare Questionnaire (PHQ-9), which assesses suicidal ideation, we have developed a safety plan for anyone who answers positively to question 9 on the PHQ-9 (see Steps taken to minimize risk below).

Adverse event definition:

This is an observational study of medically and surgically ill patients undergoing open-heart surgery, and this population—independent of this study—is at significant risk for a range of medical and surgical complications because of their underlying heart disease, open-heart surgery, and care provided during the perioperative period. In this study, we define an adverse event as any symptom, sign, illness, or experience that develops or worsens during the study that is reasonably attributable to the study assessments or receipt of daridorexant.

Serious adverse event:

A serious adverse event is defined as any adverse event resulting in any of the following:

- Sleep paralysis (inability to move or speak when going to sleep or waking up)
- Cataplexy (discrete episode of muscle weakness, typically associated with strong emotion)
- Complex behaviors while asleep that pose danger to the patient or others (*e.g.*, sexually inappropriate acts)
- Angioedema or anaphylactic reaction to daridorexant
- Death/suicide
- Prolongation of existing hospitalization
- Persistent or significant disability or incapacity
- Medical or surgical intervention required to prevent permanent impairment or damage

Recording adverse events:

Each adverse event—whether observed by the PI or elicited from or volunteered by the subject—will be documented. Each adverse event will include a brief description of the experience, the date of onset, the date of resolution, the duration and type of experience, the severity, the nature of any potential relationship to study assessments, contributing factors, and any action taken with respect to the assessments. Any such adverse event will be reported to the Data and Safety Monitoring Advisory Council (see **16. Data and Safety Monitoring Plan**).

Responsibilities for reporting serious adverse events:

The PI will record all serious adverse experiences that occur during the study period in the appropriate source documents and/or adverse events log as applicable. The timeframe for adverse event reporting will begin from the time of study enrollment to the final study assessment on POD 3 (or on a subsequent postoperative day for those with delirium on POD 3).

Steps taken to minimize risk:

We will adhere to the exclusion criteria listed above which will help avoid the recruitment of patients most at risk of side effects and adverse consequences. Patients will be interviewed each day for any side effects and the medical records will be reviewed and the data collected for Aim 4 of this study.

Risks pertaining to clinical assessment:

The risks pertaining to clinical assessment (neuropsychological testing and questionnaires) are anticipated to be no more than minimal. If the patient exhibits any distress or hesitation in answering specific

questions or completing a questionnaire in general, the evaluation will be suspended and the subject asked whether they wish to either take a break, skip a given section, or withdraw from the study. The PI Dr. Oldham is a board-certified psychiatrist with clinical expertise in mental health evaluation. If he is conducting the assessment, he will use his medical judgment to determine whether to suspend evaluation or skip portions of the interview. If study personnel are conducting the evaluation, they will be instructed to contact Dr. Oldham to join the interview and conduct additional assessment as necessary to determine whether the interview should be suspended or modified.

Similarly, if a patient responds affirmatively to question 9 on the PHQ-9, which asks about "Thoughts that you would be better off dead, or of hurting yourself," the PI will conduct a safety evaluation to determine whether the patient should be referred for immediate clinical attention. (This will be done by the PI Dr. Oldham at the time of the evaluation if he is completing the evaluation. If the evaluation is being conducted by research personnel, a licensed clinical member of the study team will be contacted, and they will join the interview either in person or remotely to conduct a safety evaluation.) If, in the clinical judgment of the PI, the patient is assessed to be at imminent risk of self-harm, we will ensure appropriate emergency care for safety. Because this study is enrolling outpatients who have agreed to undergo a life-preserving, function-enhancing surgery, we expect the likelihood that any subject will be acutely suicidal will be *exceptionally low*.

See below **CONFIDENTIALITY OF DATA AND INFORMATION STORAGE** > Risks pertaining to data transmission for protection against potential disclosure of data analyzed using Esprit Nova.

Risks pertaining to study participation:

Study personnel will not enter results of assessments into a patient's medical record; however, study participation would entail that their treatment team are aware of the clinical trial and be responsible for ordering study drug for the three first postoperative nights. The fact that the patient is in the study will be included in the patient's medical record. Study team members will provide education to all providers of study subject teams so that they are aware (1) of the clinical trial, (2) the study methods, (3) their need to order study drug for the first three postoperative nights, and (4) their responsibility to report to the PI any potential adverse events and serious adverse events as defined in this trial.

A DSMB will review the data (as described below) and the study will be halted if there is evidence of harm significantly associated with the intervention. We will also inform subjects of the risks of daridorexant in the consent form and ask them to notify their treatment team at SMH should they experience any serious adverse events.

Plan for reporting unanticipated problems or study deviations:

All AEs and SAEs will be reported to the RSRB and DSMB as required. Data on adverse effects will be collected each postoperative day that subjects are enrolled.

Plan for breaking the blind for a subject

If a patient has a medical emergency that requires immediate clinical care for stabilization, including angioedema, anaphylaxis, attempted suicide, or any other condition that is considered—in the opinion of the PI or the primary medical team—as potentially attributable to daridorexant, we will contact the IDS pharmacist to identify whether the patient has received daridorexant or placebo. If this occurs, the subject will be withdrawn from the study, and this will be reported to the RSRB and DSMB.

Legal risks such as the risks that would be associated with breach of confidentiality:

As with any study incorporating research into clinical care, there is a small but real risk of unintentional release of HPI. We will make every effort to secure data and study records under double lock/key and encryption in keeping with institutional standards to prevent this from occurring.

10. POTENTIAL BENEFITS TO SUBJECTS

There is no anticipated benefit to subjects who take part in this research study.

11. COSTS FOR PARTICIPATION

There are no anticipated costs for study participation.

12. PAYMENT FOR PARTICIPATION

Study subjects will be compensated $50 by check sent from the University of Rochester Medical Center to that subject's home address. Study medication—either daridorexant or placebo—will be provided and administered free of charge to the patient.

13. SUBJECT WITHDRAWALS

Definition of treatment failure or subject removal criteria:

All consented subjects will be retained in the study, and all primary analyses will be performed per protocol. All daridorexant arm subjects who develop postop delirium represent patients for whom daridorexant failed to prevent delirium. However, we do not expect daridorexant to prevent all delirium, so we would not use the term "treatment failure" to describe incident delirium in these patients. We would remove patients from the study only in the event of serious adverse events.

What happens to subjects when study ends or if a subject's participation in the study ends prematurely:

Patients will be thanked for their participation in the study and will be advised to call the PI with any questions. Study agent—either daridorexant or placebo—is being provided for up to the first three nights after surgery, but we will not be providing this to those who discharge prior to this. Early discharges are not only rare but indicate that the patient is doing so well that they no longer require inpatient level of care, which implies that they would not have delirium at the time.

14. PRIVACY AND CONFIDENTIALITY OF SUBJECTS AND RESEARCH DATA

See also Appendix I – University of Rochester Human Subject Research Electronic Data Security Assessment Form

Risks pertaining to confidentiality of data and information storage:

Study data will be collected confidentially from the patient and collateral informant. Patients will be assigned a sequential study identification number, which is used for all study purposes. Data from interviews and self-report questionnaires including consent forms will be recorded in hardcopy. All hardcopies will be permanently stored in a locked filing cabinet at SMH either in the PI's personal office or the office of study personnel. Name, date of birth, and other identifying information will be kept in a separate locked file. All data will be entered into an electronic database (REDCap, described in next paragraph) into a final dataset that will be de-identified and reside on a secure URMC server. Study personnel will have access to research data. In performing analyses, the PI may share de-identified data with any member of the mentorship team for guidance on analyses.

Study data will be collected and managed using Research Electronic Data Capture (REDCap) tools hosted at URMC.[104] REDCap is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data

manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

15. DATA / SAMPLE STORAGE FOR FUTURE USE

De-identified data will be stored indefinitely both for subsequent analyses and to support anticipated future grant applications. The data will be stored on the PI's office UR computer, UR research laptop, in a UR Box folder, and in REDCap. Upon study completion, only the PI will have direct access to de-identified study data.

16. DATA AND SAFETY MONITORING PLAN

Overview:

This Data and Safety Monitoring Plan (DSMP) specifies the procedures and rationales of the current prospective trial to ensure the safety of subjects and the validity and integrity of the data collected. The DSMP identifies who will look at the data and review any adverse events, how often, and what they are authorized to do.

For this study, the PI will be responsible for monitoring the project as the Data and Safety Monitor under advisement of an independent Data and Safety Monitoring Board (DSMB). All adverse events will be recorded and reports created by the PI in collaboration with the research coordinator.

The DSMB will include individuals with clinical experience relevant to this population and sleep pharmacology.

The risks associated with this trial are described in section 9 above.

Data and Safety Monitor:

As the Data and Safety Monitor, the PI will be responsible to maintain protocols and consent documents for this study, monitor safety issues throughout the study, and provide an overview of the quality of the accumulating data. DSM Monitor responsibilities and actions include:

a. Review and approve, disapprove, or suggest modifications to the study protocols and/or consent documents to assure both scientific integrity and study adherence to human subject protection policies.
b. Monitor, provide feedback, and report on scientific and ethical issues related to study implementation for the protection of human subjects and advise on ethical issues related to adverse events.

Data and Safety Monitoring Board:

a. The DSMB will monitor adverse event reports for purposes of determining whether their nature, frequency and severity are consistent with expectations.
b. The DSMB, in coordination with the PI, will report to the Research Subjects Review Board any unanticipated problems involving risks to subjects (per 45CFR46). If considered related to the study, adverse events involving risks to subjects or to others must be reported by the PI to the University of Rochester Research Subjects Review Board.
c. The DSMB can recommend remedies or other appropriate actions such as introducing new monitoring protocols, altering inclusion or exclusion criteria, or recommending changes in the informed consent documents.

d. Ensure that the study protocol maintains patients' confidentiality in a manner that is appropriately balanced with issues of clinical care and safety.
e. Monitor data management activities. The DSMB may ask to review data relevant to quality control. This Board will review requests for interim analyses and approve, disapprove, require additional information, or defer decisions.

Schedule:

The DSMB will review study conduct and data collected after the first six enrolled subjects have completed the study and then again after the full study sample of 12 subjects have completed the study. Given block randomization with a block size of six, we expect the initial review of six subjects will include three subjects receiving daridorexant and three receiving placebo. The DSMB and study PI will decide the format of meetings. Additional meetings or telephone conferences will be held on the recommendation of the DSMB.

17. DATA ANALYSIS PLAN

The first 3 aims outlined for this study pertain to the viability of the currently outlined study methods and do not avail themselves to formal statistical analysis. We will collect these data to inform an anticipated follow-on RCT of daridorexant to prevent postoperative delirium.

Aim 4 pertains to AE and SAE, which are also essential for the investigational application of daridorexant to delirium prevention. The rates of AE reported with daridorexant are extremely low and very nearly close to placebo in published studies. These will be collected for this feasibility study, although we do not expect to identify concerns.

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