A Preliminary Study of Prophylactic Fentanyl Sublingual Spray (FSS) for Exercise-Induced Breakthrough Dyspnea

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A. Study Objectives

Primary objective:

To determine the **effect of prophylactic fentanyl sublingual spray** (FSS, 15-25% and 35-45% proportional doses) on the **intensity of exercise-induced dyspnea** (modified Borg scale) between the first and second shuttle walk tests. *We aim to estimate the effect size for both FSS arms to inform a larger, adequately powered confirmatory randomized controlled trial.*

Secondary objectives

A.2. To determine the **effect of prophylactic FSS** (15-25% and 35-45% proportional doses) on **walk distance and adverse effects** between the first and second shuttle walk tests. *We hypothesize that FSS is superior to no FSS in increasing walk distance and has limited side effects in opioid tolerant individuals.*

A.3. To compare the **intensity of exercise-induced breakthrough dyspnea** between high (35-45% proportional dose) and low (15-25% proportional dose) doses of prophylactic FSS. *We hypothesize that higher doses of FSS is superior to lower doses FSS in reducing dyspnea at the end of the shuttle walk test.*

B. Background

Dyspnea is a subjective awareness of difficulty breathing, which may be associated with the distressing sensation of suffocation. It is one of the most common and most feared symptoms among cancer patients, occurring in up to 70% of patients in the last 6 weeks of life [1,2]. Dyspnea is associated with fatigue, anxiety, decreased function and quality of life, and increased mortality [3,4].

In a study examining 70 patients with dyspnea, 43 (61%) reported breakthrough (episodic or incidental) dyspnea only, 13 (19%) had constant dyspnea only, and 14 (20%) experienced both constant and breakthrough dyspnea. A substantial proportion of the patients with breakthrough dyspnea (18/57, 32%) presented with 5 or more episodes per day, and the majority of episodes lasted <10 minutes [5]. Breakthrough dyspnea is particularly challenging to treat because of its transient and episodic nature.

Exercise-induced dyspnea (or shortness of breath on exertion) is a subtype of breakthrough dyspnea. Breakthrough dyspnea has 4 major triggers: exertion, emotional changes, the environment (e.g. altitude, smog), and spontaneous/idiopathic. Because many cancer patients experience severe shortness of breath with activities (i.e. walking), they have to limit their function significantly. In a recent study conducted by our group, we found that a vast majority of patients (81%) had breakthrough dyspnea. Specifically, dyspnea affects patients' general activity, walking ability, normal work, sleep, mood, relations with others and enjoyment of life [5].

The current management of dyspnea involves treatment of any reversible causes and supportive measures to minimize the sensation of dyspnea, such as oxygen, opioids, bronchodilators, and corticosteroids [1,6,7]. A majority of the studies on cancer-related dyspnea so far focused on patients with dyspnea at rest. In a cross-over randomized controlled trial, Bruera et al. compared subcutaneous morphine and placebo in 10

patients with advanced cancer who had dyspnea at rest. Subcutaneous morphine was found to be superior to placebo for relief of dyspnea [8]. This finding was replicated by Mazzocato et al. in another randomized controlled trial with similar design [9]. A Cochrane meta-analysis also showed a statistically significant positive effect of opioids on the sensation of breathlessness (p=0.0008), supporting the use of oral or parenteral opioids for treatment of dyspnea in patients with advanced disease [7,10]. Several other systematic reviews have confirmed this finding [1,11].

Treatment options for breakthrough dyspnea. Although systemic opioids are established for management of dyspnea at rest, there are currently no definitive evidence-based options for breakthrough dyspnea. In a case series, Bruera et al. reported the use of rescue morphine given subcutaneously for 312 episodes of breakthrough dyspnea in 45 cancer patients. After 30 minutes, 90% reported no to mild dyspnea [8]. Based on this study, most clinicians use a dose similar to the rescue opioid dose for breakthrough pain (i.e. 10-20% of total daily dose) to manage breakthrough dyspnea. However, a more recent double-blind randomized controlled trial comparing systemic hydromorphone (oral or subcutaneous (SC)), nebulized fentanyl, and nebulized saline for breakthrough dyspnea found no significant difference in dyspnea relief at 10 minutes between the treatment arms [12]. One of the reasons may be due to the short duration for the primary endpoint (10 minutes) and the fact that the investigators used mostly oral hydromorphone, which reaches peak concentration only 45-60 minutes later. We recently completed a preliminary study examining the role of subcutaneous fentanyl for breakthrough dyspnea, and found a significant improvement in both dyspnea scores and walk distance before and after the study [13]. To date, the evidence for opioid use for breakthrough dyspnea in cancer patients remains limited (Table 1). A recent review on the role of opioids in breakthrough dyspnea supported a promising therapeutic effect in cancer and non-cancer settings [14]. Further research is necessary to improve the management of this distressing and debilitating symptom.

Table 1. Studies of Opioids for Breakthrough Dyspnea in Cancer Patients

Study	Methodology and patients	Agent and dose	Outcome
Bruera et al. Ann Intern Med 1993 [8]	Prospective case series (45 cancer pts)	SC morphine 312 doses given (same dose as pain breakthrough)	After 30 minutes, 90% reported no-mild dyspnea; 5% mod-severe dyspnea
Benitez-Rosario et al. JPSM 2005 [15]	Retrospective case series (4 cancer pts)	OTFC 800mg/1200mcg 60mg/800mcg 120mg/600mcg 15mg/400mcg	RR decreased Dyspnea decreased by 90-100% in 20-60 minutes
Sitte et al. JPSM 2008 [16]	Retrospective case series (1 cancer pt, 2 heart failure pts)	Intranasal fentanyl 1/6 of MEDD	RR decreased, improved O_2 saturation in all 3 patients Dyspnea scores not reported
Gauna et al. JPM 2008 [17]	Prospective case series (2 COPD pts, 2 cancer pts) 10 episodes	OTFC 30mg/200mcg 720mg/400mcg 20mg/200mcg	RR decreased Dyspnea decreased by 90-100% in 20-60 minutes

		24mg/200mcg	
Charles et al. JPSM 2008 [12]	Prospective, double blind crossover RCT (20 cancer pts)	Systemic (mostly oral) hydromorphone Nebulized hydromorphone Nebulized saline	Dyspnea decreased similarly in all 3 arms (1.0, 0.9, 0.8)
Hui et al. JPSM 2014 [13]	Prospective, double blind crossover RCT (20 cancer pts)	Subcutaneous fentanyl Nebulized hydromorphone Nebulized saline	Dyspnea and walk distance significantly improved in the fentanyl arm

Abbreviations: RR=respiratory rate, OTFC=oral transmucosal fentanyl citrate, SC=subcutaneous

The role of rapid onset opioids. The episodic and transient nature of breakthrough dyspnea makes fast onset opioids an attractive option. Administration of opioids intravenously or subcutaneously can allow rapid delivery of the drug, although many patients do not have access to these routes at home. Fentanyl is a highly lipophilic compound. Over the past decade, there has been active development of fentanyl, including delivery by the transmucosal (oral transmucosal fentanyl citrate [OTFC], Actiq), buccal (Fentora), intranasal (Lazanda, Instanyl) and sublingual (Subsys, Abstral) formulations [18-20] These fentanyl formulations have been successfully used to manage breakthrough pain [21-28], although their role in breakthrough dyspnea has only been reported in a handful of studies. Two small retrospective case series reported on the use of transmucosal and intranasal fentanyl [15,16] and one prospective series examined the use of OTFC [17] suggest significant improvement in breakthrough dyspnea with these agents. Randomized controlled trials are urgently needed to confirm these findings with rapid onset opioids, which could potentially open up a new therapeutic indication for these medications.

Fentanyl sublingual spray (FSS) is a particularly attractive option for breakthrough dyspnea. It was approved by the US Food and Drugs Administration in 2012 for “the management of breakthrough pain in adult cancer patients who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain”, and represents an alternative delivery system for fentanyl that also utilizes a transmucosal route like OTFC. A pharmacokinetic study examining 5 different doses of FSS (100 mcg, 200 mcg, 400 mcg, 600 mcg, 800 mcg) in healthy volunteers demonstrated that fentanyl enters the systemic circulation rapidly, achieving 27%, 61%, 87% and close to 100% of maximal plasma concentration (Cmax) within 5, 10, 20 and 30 minutes, respectively [29]. In a separate crossover study comparing FSS 400 mcg, OTFC 400 mcg and intravenous fentanyl 100 mcg in healthy volunteers, FSS had a greater bioavailability (76% vs. 51%) and achieved a higher Cmax than OTFC (0.81 mg/ml vs. 0.61 ng/ml). Similar to the previous study, the mean plasma concentrations were 19% and 54% of Cmax within 5 and 10 minutes [30]. In a double-blind, randomized placebo controlled trial, FSS provided greater and more rapid pain relief, and significantly reduces pain compared to placebo at 5, 30 and 60 minutes [28]. The most common adverse effects included nausea (7%), hyperhidrosis (5%) and peripheral edema (5%).

Significance. We expect to advance the understanding of how FSS can be used to treat exertional dyspnea in cancer patients. The effective management of dyspnea may ultimately help alleviate this devastating symptom. A better fundamental understanding of how this intervention improves physiologic parameters could also shed light on the pathophysiologic characteristics of dyspnea and allow us to devise new and more effective treatments.

This contribution will be significant because it represents a key step in a continuum of research that is expected to lead to the optimization of FSS to relieve exertional dyspnea in cancer patients and to improve their function and quality of life. If the preliminary results from this randomized trial demonstrate a significant effect with FSS, the next step will be to conduct a larger, multi-institutional randomized controlled trial that is adequately powered. Further confirmation of FSS's efficacy would pave the way for using this medication for a novel indication. The proposed study has the potential to greatly improve patients' symptom burden, function and quality of life, and shift the paradigm for symptom research.

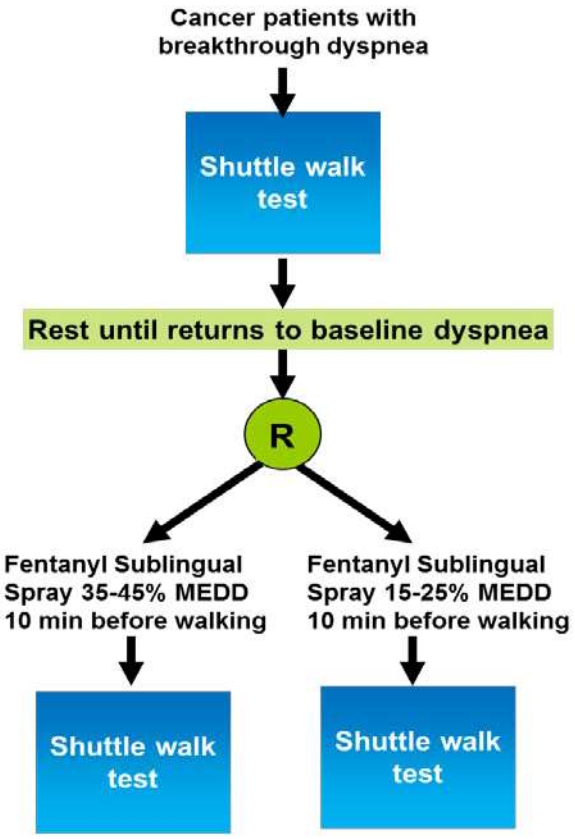

Figure 1. Study Flow Chart

C. Experimental Approach

C.1. Overall Study design. This is an investigator-initiated study supported by Insys Therapeutics Ltd. We propose a 2-arm, double-blind, parallel randomized controlled trial of FSS for cancer patients with breakthrough dyspnea (Figure 1). The main goal of this study is to determine the effect size of FSS on dyspnea (at two different doses) to inform a larger, adequately powered confirmatory randomized controlled trial. After study consent, eligible patients will be asked to complete a number of surveys and a shuttle walk test at baseline, rest until they return to baseline dyspnea, and then do another shuttle walk test after they have been given FSS prophylactically.

Based on our experience conducting symptom control trials, this study will take each patient approximately 2 hours to complete in a single visit. We believe this study design is feasible and would not add undue burden for patients. Patients will be compensated with a $50 gift card and a $15 parking voucher for their time and effort after they have completed the study assessments.

C.2. Eligibility Criteria. The eligibility criteria are shown in Table 2.

Table 2. Study Eligibility Criteria

Inclusion Criteria

1. *Diagnosis of cancer with evidence of active disease*
2. Breakthrough dyspnea, defined as dyspnea with an average intensity level over the past 7 days of at least 3/10 on a numeric rating scale upon significant exertion or continuous dyspnea </=7/10 with worsening upon significant exertion
3. Outpatient at MD Anderson Cancer Center seen by the Supportive Care Service, Thoracic Medical Oncology, Cancer Pain Clinic, or Cardiopulmonary clinic
4. Ambulatory and able to walk with or without walking aid
5. *On strong opioids with morphine equivalent daily dose of 80-500 mg for at least one week, with stable (i.e. +/- 30%) regular dose over the last 24 hours*
6. Karnofsky performance status >/=50%
7. *Age 18 or older*
8. Able to complete study assessments

Exclusion Criteria

1. Dyspnea at rest >/=7/10 at the time of enrollment
2. Supplemental oxygen requirement >6 L per minute
3. Delirium (i.e. Memorial delirium rating scale >13)
4. *History of unstable angina or myocardial infarction 1 month prior to study enrollment*
5. Resting heart rate >120 at the time of study enrollment
6. Systolic pressure >180 mmHg or diastolic pressure >100 mmHg at the time of study enrollment
7. *History of active opioid abuse within the past 12 months*
8. *History of allergy to fentanyl*
9. Severe anemia (Hb <7g/L) if documented in the last month and not corrected prior to study enrollment*
10. *Diagnosis of acute pulmonary embolism within past 2 weeks*
11. *Diagnosis of pulmonary hypertension*
12. Unwilling to provide informed consent

* To minimize study burden for participation in this 2-hour study, extra bloodwork will not be drawn unless the patient already has the above lab abnormalities documented and need to be corrected.

C.3. Study screening. A 2 step consent process will be used. First, a verbal consent will be obtained by the study staff to proceed with screening of potential participants for eligibility and to characterize their dyspnea using the dyspnea survey and the cancer dyspnea scale. Outpatients may be contacted by phone within 1 week prior to their scheduled clinic visit to inform them of this study so they can make necessary arrangements if interested in participating. Eligible patients will then be formally enrolled onto the study after they have signed the informed consent indicating a willingness to participate in the trial. The number of patients screened, approached, eligible, and enrolled will be documented. Reasons for refusal for eligible patients will also be captured.

C.4. Randomization. Patient randomization will be conducted through the Clinical Trial Conduct (CTC) website (https://biostatistics.mdanderson.org/ClinicalTrialConduct), which is maintained by the Department of Biostatistics at MD Anderson Cancer Center. The trial statistician will train the users (pharmacists or research nurses) in the use of this website for randomizing patients. The methodology to replace a patient who does

not take the study medication is as follows: In CTC, edit the patient to be replaced modifying MRN within the specific patient's stratum. Then add a history of the changes made to the Notes section. Randomization will be 1:1 between the two study arms with permuted blocks, and stratified by baseline level of dyspnea modified Borg scale at rest at the time of enrollment (i.e. 0-3, 4-6).

C.5. Blinding. Both the patient and the research staff conducting the assessment will be blinded to the treatment assignment. FSS will be dispensed by Dispensing Pharmacy at MD Anderson. Only research nurse administering the medication will be aware of the study dose, and will be instructed not to share that information with the patient and other research staff. Further to that, we will check the blinding from patients and study staff at the end of study.

C.6. Research staff. An orientation will be held with research staff involved in this study to introduce them with the study design and to standardize the provision of each intervention.

C.7. Study Interventions. The commercial supply of study medication will be provided by Insys Therapeutics Ltd. We will use a one time prophylactic FSS dose equivalent to either 15-25% or 35-45% of MEDD 10 minutes prior to the second shuttle walk test. FSS was FDA approved in 2012 for "For the management of breakthrough pain in adult cancer patients who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain."

Immediately upon patient enrollment, the study physician will be notified and will determine the morphine equivalent daily dose (MEDD) in real time using standardized equianalgesic ratios. Based on clinical practice and similarly to the dose used for breakthrough pain, we will use an FSS dose equivalent to 15-25% or 35-45% of MEDD (Table 3). The study medication will be provided by Dispensing Pharmacy and will then be administered 10 minutes before the second shuttle walk test. We estimated the FSS dose based on the following assumptions:

- A one time rescue dose 15-45% of the MEDD is safe and effective for relief of dyspnea
- FSS has approximately 70% oral bioavailability [30]

Table 3. Proportional Dosing of FSS for patients randomized to the two study arms

High dose (target 35-45% MEDD)				**Low dose (target 15-25% MEDD)**			
MEDD (mg/day)	**FSS dose***	**% of MEDD - low**	**% of MEDD - high**	**MEDD (mg/day)**	**FSS dose***	**% of MEDD - low**	**% of MEDD - high**
80-100	200	35.0	43.2	80-130	100	13.5	21.6
101-150	300	35.0	52.0	131-210	200	16.7	26.7
151-200	400	35.0	46.4	211-280	300	18.8	24.9
201-250	500	35.0	43.5	281-450	400	15.6	24.9
251-300	600	35.0	41.8	451-500	600	21.0	23.3
301-400	800	35.0	46.5				

401-500	1000	35.0	43.6

* FSS comes in 100 mcg, 200 mcg, 400 mcg, 600 mcg and 800 mcg. A combination of these products would allow us to deliver the desired dose.

The following instructions will be given to the patient:
1. Swallow any saliva in your mouth.
2. Hold the medication spray unit upright using your index and middle fingers and thumb.
3. Point the nozzle into your mouth and under your tongue.
4. Squeeze your fingers and thumb together to spray the medication under your tongue.
5. Hold the medicine under your tongue for 30-60 seconds. Do not spit out any medicine. Do not rinse your mouth.
6. The spray unit will remain locked after use.

C.8. Medication use during study. To minimize the co-intervention effect on dyspnea, patients will be advised to avoid using breakthrough opioids (for any reason) or bronchodilators for at least 2 hours prior to and during the study.

C.9. The Shuttle walk test is an externally paced test, and has been found to be high reproducible for inducing breathlessness in patients with advanced cancer [31-33]. Furthermore, the shuttle walk test was reported to be equivalent or better than 6 minute walk test in detecting a clinical response [34-36]. Shuttle walk tests will be conducted according to published procedures [31-33]. The first shuttle walk test is designed to provide important information regarding a patient's level of dyspnea on exertion, and to facilitate intra-individual comparison since there is significant variability in the expression of dyspnea among patients. The second shuttle walk test will be conducted 10 minutes after study medication has been administered.

The research staff conducting the walk test must be certified in cardiopulmonary resuscitation with a minimum of Basic Life Support by an American Health Association–approved cardiopulmonary resuscitation course. Walking aid is allowed as long as patients keep them the same as before enrollment and during the entire study.

The shuttle walking test requires the patient to walk up and down a 10 m course. The course will be identified by two cones inset 0.5 m from either end to avoid the need for abrupt changes in direction. The speed at which the patient walks will be dictated by an audio signal played on a tape cassette. The start of the test will be indicated by a triple bleep. Thereafter the tape will emit a single bleep at regular intervals, at which point the subject will attempt to be at the opposite end of the course-that is, by the time the patient heard the signal he should be turning round the cone to proceed back down the course. After a minute on the same level, the subject will proceed to the next level with the speed of walking increased by 0.167 m/s (or 10 m/min). A change of speed to the next level will be indicated by a triple bleep from the tape recorder (Table 4).

To help the patient to establish the routine of the test and the first, very slow, speed of walking, the operator will walk alongside for the first minute. The patient will have 20

seconds to complete each of the three shuttles in the first minute. After this first minute patients will pace themselves to coordinate their walking speed with the timed signals. When patients reached the cone before the signal, they will be instructed to remain until the signal indicated that they could proceed with the test.

Table 4. Shuttle walk test levels

Level	*Speed (m/s)*	*Time required for 10 m course (s)*	*Number of shuttles per level*	*Total time in each level (s)*	*Cumulative distance walked (m)*
1	0.500	20	3	60	30
2	0.667	15	4	60	70
3	0.833	12	5	60	120
4	1.000	10	6	60	180
5	1.167	8.57	7	60	250
6	1.333	7.5	8	60	330
7	1.500	6.67	9	60	420
8	1.667	6	10	60	520
9	1.833	5.45	11	60	630
10	2.000	5	12	60	750
11	2.167	4.62	13	60	880
12	2.333	4.29	14	60	1020

The explanation to the patient will be standardized (see appendix). Patients in previous studies found it easy to pace themselves and no difficulties were encountered in administering the test.

The end of the test will be determined by either (a) the patient, when he or she was too breathless to maintain the required speed or (b) the operator, if the patient failed to complete a shuttle in the time allowed (that is, was more than 0.5 m away from the cone when the bleep sounded).

We will be assessing the dyspnea level with modified Borg scale at baseline and then every minute during at the shuttle walk test as well as at the end. We will also measure the heart rate, respiratory rate, blood pressure, oxygen saturation before and immediate after the shuttle walk test. The total walking time and distance will also be measured. We will also ask the reasons for stopping or being unable to keep up with the required pace using a standardized statement and question: “You had to stop, what was it that made you stop the test?” The patients’ comments were recorded verbatim.

C.10. Variable rest period. After the first and second shuttle walk test, patients will be asked to sit down and rest. How long they rest would depend on when they return to baseline level of dyspnea + 1 or below (e.g. if baseline dyspnea = 4, they need to return to a level of 5 or less to qualify for next stage) and baseline level of fatigue +1 or below. During this rest period, patients will be assessed every 5 minutes to check their dyspnea and fatigue level. If their dyspnea/fatigue level met criteria and they feel ready

to walk again, they will be given the study treatment and asked to wait for 10 minutes before they do the second walk.

C.11. Stopping rules. In the unexpected situation in which patients do not develop any increase from their baseline dyspnea after the first shuttle walk will not proceed to the next stage because of the lack of exercise-induced dyspnea. If at any time during the study patients develop chest pain, severe leg cramps, staggering, diaphoresis, and/or dizziness, they will be asked to stop the study. If patients require more than 1 hour of rest and their dyspnea and fatigue level still has not returned to baseline, they will also be taken off study. Patient dropouts and walk test failures prior to the administration of drug will be replaced.

C.12. Study assessments. See Table 5 for a detailed description of all study assessments.

Table 5. Summary of Study Assessments

Assessments	Baseline	After 1st shuttle walk test	Rest Period	Before 2nd shuttle walk test	After 2nd shuttle walk test
Demographics and cancer diagnosis[1]	✓				
Medication history[2]	✓				
Karnofsky performance status, spirometry testing, and inspiratory pressure[3]	✓				
Edmonton Symptom Assessment Scale[4]	✓				
Dyspnea Survey[5]	✓				
Cancer Dyspnea Scale[6]	✓				
O_2 saturation and respiratory rate	✓	✓		✓	✓
Dyspnea Borg/fatigue scale[8]	✓	✓	✓	✓	✓
Dyspnea Numeric Rating Scale[7]	✓	✓		✓	✓
Walking test parameters[9]		✓			✓
Adverse effects[10]				✓	✓
Neurocognitive testing[11]		✓			✓
Global assessment, study satisfaction and blinding[12]					✓

[1] patient initials, medical record number, date of birth, sex, race, education, marital status, cancer diagnosis, co-morbidities, cause(s) of dyspnea, bedside spirometry and maximal inspiratory pressure.
[2] medications that could be used to treat dyspnea, including scheduled and as needed opioids, bronchodilators, and steroids will be documented.
[3] an 11-point assessment scale that rates patients' functional status between 0% (death) and 100% (completely asymptomatic) based on their ambulation, activity level, and disease severity [37].
[4] validated questionnaire that measures 10 common symptoms in the past 4 hours (pain, fatigue, nausea, depression, anxiety, drowsiness, shortness of breath, appetite, sleep, and feeling of well being) using numeric rating scales [38].
[5] characterization of patients dyspnea including the following: presence of dyspnea at rest, average dyspnea in last 24 hours, worse dyspnea in last 24 hours, best dyspnea in last 24 hours, number of episodes of exacerbation per day, triggers of breakthrough dyspnea, average duration of each episode, current treatment for breakthrough dyspnea.
[6] validated 12-item questionnaire specifically designed to assess the quality of dyspnea in

cancer patients during the past few days [39]. Each item has a score between 1 and 5, for a maximum of 60. There are sub-scores for sense of effort, anxiety, and discomfort.
[7] a 0 to 10 categorical scale for rating the severity of dyspnea. It is a ratio scale with descriptive anchors throughout the range in which a rating of 8 signifies breathlessness twice as severe as 4, which in turn is twice as severe as 2 [40-43]. We will be measuring it every minute during the shuttle walk test starting from 0 minutes until the end of walk. This will be the primary endpoint because it has good reliability and validity for assessing dyspnea [40,41,44] and has been used in multiple other studies on exertional dyspnea [45-48]. The minimal clinically important difference is 1.0 in patients with chronic obstructive pulmonary disease [49]. This scale can be administered quickly, and was found to be easy to use by patients [41]. In a study that compared the dyspnea modified Borg Scale, numeric rating scale and visual analog scale, the modified Borg scale was preferred by participants and was recommended as the best tool to quantify dyspnea intensity [50]. Furthermore, its use is recommended by the American Thoracic Society and American College of Chest Physicians for Cardiopulmonary Exercise Testing [51].
[8] a 0 (no dyspnea) to 10 (worst dyspnea) categorical scale validated for rating the severity of dyspnea [40,42,43]. The intensity and unpleasantness of dyspnea will be measured using the Borg scale 10 minutes prior to the shuttle walk test, every minute during the shuttle walk test until the end of the walk, and immediately after each shuttle walk test
[9] include the total distance walked, total walking time, the distance and time of first rest due to dyspnea, average walking speed.
[10] adverse effects related to the use of FSS, such as dizziness, drowsiness and nausea will be assessed using a numeric rating scale from 0-10.
[11] patients will be asked to do a finger tapping test, simple math test, reverse memory of digits, and visual memory). This has been used in other studies by our group.[52]
[12] patients will be asked about their dyspnea (worse, about the same, or better) comparing between the level of dyspnea between the first and second shuttle walk tests [53,54]. Study satisfaction will be assessed with the following questions, “Was it worthwhile for you to participate in this research study?”, “If you had to do it over, would you participate in this research study again?”, “Would you recommend participating in this research study to others?”, “Did you quality of life get better by participating in this research study?”, and “Did your quality of life get worse by participating in this research study?” Blinding will be assessed by asking patients and study staff which group assignment they believe they received: “high dose”, “low dose”, or “do not know”.

C.13. Feasibility data. In addition to clinical outcomes, we will also collect feasibility data in this study, including the following:

- Rates of recruitment and retention (% of subjects able to complete the study)
- Reasons for refusal and dropout
- Participant satisfaction—participants will provide an opinion regarding their satisfaction with study overall

C.14. Patient Safety, Monitoring, and Confidentiality.

During the study, both a research nurse and a research coordinator will be available to perform study assessments and provide safety monitoring. This study will be conducted right outside our Supportive Care Center, where we have additional support from multiple clinic nurses and doctors. The cardiopulmonary center is also very close. If desaturation occurs, we will put patient on supplemental oxygen, and determine if the patient becomes non-hypoxemic after

a short rest. In the unexpected event in which the patient requires oxygen beyond nasal cannula or have prolonged hypoxemia at rest (>30 minutes), we will send the patient to ER for further assessment. Based on our experience conducting similar studies on exertional dyspnea in which we routinely monitor their vitals, there is a minimal risk of significant saturation with exercise. A study physician will also be available by pager to address any concerns, distress, or questions, and will attend to the patient as needed. See stopping rules above for further details.

Regulatory monitoring will be provided by the principal investigator and the Institutional Review Board (IRB). Patient confidentiality will be ensured by use of study numbers, secure storage of clinical data, and anonymous reporting.

Research-Related Injury
Insys will be responsible for payment of the actual and reasonable medical expenses incurred in diagnosing and treating any injury, illness or adverse reaction of a study subject that results from the administration of Fentanyl Sublingual Spray.

C.15 Serious Adverse Event Reporting (SAE) Reporting
Serious adverse events will be captured from the time of the first protocol-specific intervention, until 14 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

D. Statistical Analysis

D.1. Power Calculation. This pilot study is based on a sample of 15 evaluable subjects per arm, for a total of 30 patients. We expect to enroll approximately 2-3 patients per month for this study. Thus, we expect to complete the study in approximately 10-12 months.

The primary objective of determining effect size for powering future studies is collecting data on the distributional properties of dyspnea scores for the two arms. This study is not powered to test differential treatment effects between the two treatment groups measured by dyspnea modified Borg scores. Instead, with 15 patients in each group, we will have an 80% power to detect an effect size of 0.778 in difference of the dyspnea modified Borg score change after a shuttle walk test before and after the treatment (i.e., between the first and second shuttle walk) using a two-sided paired t-test with a significance level of 0.05.

D.2. Data Analysis. Summary descriptive statistics will be provided for demographics, outcomes, and other collected variables such as the change of exercise induced dyspnea, walk distance, neurocognitive function and various physiological parameters at the end of each walk and the difference of these changes between two walks, and will include proportions, medians, means, 95% confidence intervals, and other simple statistics as appropriate for the measure. Each endpoint will be evaluated repeatedly

during the 1st and 2nd walk tests when appropriate. Repeated measures analysis may be employed to evaluate the change of these measures over time during each walk. We will also evaluate the effect of distance walked on the dyspnea in the repeated measures analysis, when possible. The effect of treatment on the changes of these measures will also be estimated in the same model when possible. Other statistical methods may be applied when appropriate.

E. Data Confidentiality Procedures

Health information will be protected and we will maintain the confidentiality of the data obtained from the patients' charts.

Collection of identifiers: We will collect and securely store patients' identifiers (including name, medical record number, and demographic specifications). Each patient will be assigned a study number that will be the only identifier to figure in the analytical file and personal data will not be disclosed in any form. The key linking these numbers will be retained in a securely locked file by the investigator.

Data Storage: Protection of electronic and paper records will be maintained to the best of our ability. All electronic records will be stored on password-protected institution computers behind the institution firewall. Any paper records will be classified and stored in locked files inside a locked office.

Training of personnel: Only MDACC personnel trained in maintaining confidentiality, the principal investigator, co-investigators, collaborators, and research staff will have access to study records.

Data sharing: Study data will not be shared with any individuals or entities without prior IRB-approval. The data will be kept by the principal investigator in a locked file cabinet or password-protected computer.

Final disposition of study records: Once the research has been completed, identifiers will be retained for as long as is required by law and by institutional regulations, and at that point will be destroyed. PHI may be maintained indefinitely, aggregated in the future, and used for future research studies.

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