Western Sydney University – NICM Health Research Institute

Participant Information Sheet/Consent Form

Interventional Study - *Adult providing own consent*

Title	A Double-blind, Randomized, Placebo-controlled, 4-arm Parallel-group, Multiple-Dose Study to Assess Efficacy and Safety of Medical Cannabis Aerosol via the Fixed-dose Syqe Inhaler as an Add-on Treatment of Diabetic Peripheral Neuropathic Pain.
Protocol Number	Syqe-004
Global Project Sponsor **Local Project Sponsor**	Syqe Medical Ltd. Syneos Health Australia Pty Ltd
Principal Investigator	Dr Oit Holtzman Assif
Associate Investigator(s) *(if required by institution)*	
Location *(where PI will recruit)*	Western Sydney University – NICM Health Research Institute. 158 Hawkesbury Road, Westmead, NSW, 2145

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in a research study because you have diabetic peripheral neuropathic pain. The research project is testing a potential new treatment for diabetic peripheral neuropathic pain. The treatment is called Syqe Fixed-dose Inhaler delivering delta-9-tetrahydrocannabinol (also known as Δ^9-THC) which is assumed to be the principal psychoactive compound in cannabis. You will be unable to participate in this study if you have used cannabis products within the last 3 months or if you had drug or alcohol abuse within the 12 months.

This Participant Information Sheet Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not to take part.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

- Understand what you have read
- Consent to take part in the research project
- Consent to have the tests and treatments that are described
- Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

2 What is the purpose of this research?

The purpose of this study is to see how well the study treatment, a drug-device combination ("the study treatment) called Syqe Fixed-dose Inhaler performs as a possible treatment for diabetic peripheral neuropathic pain. The Syqe Fixed-dose Inhaler is a portable, hand-held, battery operated, software controlled device. It heats medical grade cannabis and delivers a fixed-dose aerosol. If you are considered suitable to participate in the study you will receive a kit, containing the inhaler, a mouthpiece and a charging cable and power adapter. In addition, you will receive a separate box, containing a rigid case to protect the inhaler when it is not used or charged. A cartridge inside the inhaler consists of 60 chips containing the medical grade cannabis. At each site visit, the used cartridge will be removed and a new one will be placed in the device by the study staff. After 3 cartridges have been used, the study staff will also replace the mouthpiece on the device. Upon inhalation through the mouth, aerosol is rapidly absorbed through the lungs into the blood stream. The cannabis derived aerosol is assumed to reduce diabetic pain.

The Syqe fixed-dose Inhaler is an experimental treatment. This means that it is not an approved treatment for diabetic peripheral neuropathic pain in Australia, the United States or the European Union.

This research is being conducted by Syqe Limited and sponsored in Australia by Syneos Health Australia Pty Ltd.

3. What does participation in this research involve

The main purpose of this study is to learn how well the study treatment works and how safe it is compared with placebo. A placebo is a medication with no active ingredients or a procedure without any medical benefit. It looks like the real thing but is not.

This study is divided into 4 periods: a screening period (1), an up-titration period (2) (dose starts off low and increases to maintenance dose automatically by the device), a maintenance treatment period (3) (when you have reached your target dose on which you will continue for 12 weeks), and a follow-up period (4) after study treatment has finished.

During each study period, you will have visits with your study doctor and/or study coordinator at the site and will receive phone calls from the site.

The screening visit will last about 1.5 hours, and all other visits at the site will last between 1-3 hours.

Before any study-related tests and procedures can be done, you will be asked to read and sign this informed consent form, then the study will begin with a screening visit. The purpose of the screening visit is to decide whether or not this study is suitable for you. If this study is not suitable, the study doctor will explain why and will discuss other treatment options with you.

If the study doctor decides that you meet all the requirements to be in this study, you will be randomly assigned (by chance) to receive 1 of the following treatments and receive the Syqe Fixed-dose Inhaler and accessories (as described above):

- Aerosol containing 0.25 milligram (mg) of Δ^9-THC three times per day*
- Aerosol containing 0.50 milligram (mg) of Δ^9-THC three times per day*
- Aerosol containing 1.0 milligram (mg) of Δ^9-THC three times per day*
- Placebo containing 0 milligram (mg) of Δ^9-THC three times per day

* THC (tetrahydrocannabinol) is a main botanical compound of Syqe Fixed-dose Inhaler. Medical cannabis aerosol also contains other botanical compounds from the cannabis plant.

You will have a 75% (3 in 4) chance of receiving medical cannabis aerosol and a 25% (1 in 4) chance of receiving placebo. You, the study doctor, and any other people involved in the study will not know which treatment you're receiving. However, this information will be given to the study doctor if it becomes necessary for your safety. The amount of cannabis used for each inhalation is much lower than in other cannabis products that you may have experienced in the past. This might mean that the smell and taste of the aerosol will be different compared to your previous experience or expectation, but this does not mean that you are receiving placebo. Also, you may not feel an immediate relief of your pain, which may take weeks to take effect. If you don't experience improvement, please continue in the study, as the effect may take the entire duration of the study until pain perception is modified. The study doctor or study staff will give you instructions on how to use the study treatment.

During the first days as the medication dose starts off low and gradually increases to the maintenance dose (up-titration period), the study nurse will contact you daily by phone to check on your well-being and to see if you have any side effects. You will receive daily phone calls each time your dose is increased starting from second day of up-titration period (on the first day you will receive your dose while at the study site). In total, you will receive 11 phone calls during up-titration period. In addition, 2 visits to the study site will be scheduled during this period. During the maintenance period of 12 weeks, you will visit the study site every 2 weeks and receive phone calls every other week. During the 4-weeks follow-up period, you will visit the study site 3 times and the study nurse will contact you twice by phone.

Description of the procedures and assessments

At some visits you will be asked not to take your study treatment before coming to the site, so that assessments can be done before and after you take your study treatment. Your study staff will remind you before these visits not to take your study treatment. If you have taken treatment before coming to the site for these visits, you may be asked to wait for some time until some of the assessments can be done, or to come back to the site on a different day.

- Medical history, previous therapy, and demographics: Includes questions about your health, your diabetic peripheral neuropathic pain, any medicines or treatments for diabetic peripheral

neuropathic pain you are currently using or have used in the past, alcohol consumption, past and current cannabis use, smoking history, and demographics (age, sex, race, and ethnicity).

- Full physical examination: Includes checking your general appearance, ears, eyes, nose, throat, heart, lungs, abdomen (stomach), back, lymph nodes, arms and legs, skin, neck (including thyroid), vascular, neurological system, and any other notable physical conditions.
- Brief physical examination: Includes checking your general appearance.
- Vital signs: Includes heart rate, blood pressure, respiration rate, weight, height (only at screening), and body temperature.
- Electrocardiogram (ECG): Sticky patches will be placed on your chest that will be connected by wires to a machine that will record the electrical activity of your heart.
- Spirometry: A group of tests to check how well the lungs work. You will be blowing into a tube connected to a machine reading your lung function. It might take up to 8 trials within a single session.
- Laboratory tests: Blood and urine samples will be collected
    - A urine sample will be collected for safety tests to check your health and to check for the following drugs: cocaine, amphetamines, barbiturates, cannabinoids (including Δ^9-THC), opiates, phencyclidine (PCP), and methadone.
    - 212 mL of blood will be taken from a vein in the arm that will be taken over a time period of 22 weeks. For reference, the amount of blood given for a typical blood donation is 500milliliters (mL). Your blood samples are used for the following tests:
        - Approximately 92 mL (5 tablespoons) of blood will be taken during the study for various safety tests to assess your health and to check your HbA1c (long-term blood sugar level).
        - Approximately 120 mL will be taken to assess how the body processes the study drug (pharmacokinetics [PK]). This testing requires 1 blood draw before your dose at Visits 2, 7 and 9. Additionally, 1 blood draw will be taken before and up to and 3 blood draws up to 2 hours after your dose during visits 5 and 11. 1 blood sample will be taken at Visit 12.
        - Serum (blood) and urine pregnancy test: Only for women who are of childbearing age.
        - Viral test: You will be checked for hepatitis B, C, and HIV. You can only participate in this study if you have negative HIV and hepatitis test results. You will receive information and counselling before the test. If a test shows you have HIV or Hepatitis, you will have follow-up counselling and medical advice. If your test results are positive, the study doctors are required by law to notify government health authorities. Signing the consent form means that you agree to have this testing, it will not be done without your consent.

    - Questionnaires: You will answer several questionnaires, either by reading and completing questions yourself or through questions that your study staff asks you and documents your answers. These may include questions about pain and how it impacts your life, sleep, mood, and thoughts of harming yourself. With your responses, the study doctors and the Sponsor aim to understand how the study treatment may affect you and your diabetic peripheral neuropathic pain. For the questions you complete yourself, you will be provided with a specific electronic device to record the information. Some of the questions you need

to complete every day during the study in what is referred to as the 'eDiary' in your electronic device. Via this device, you will report on the following information: information about your sleep (every morning), your averaged, worst and least daily pain intensity levels (every evening), and if you needed to take any rescue/ quick-relief medication (every evening). You will be trained on how to use the electronic device and about the reminders and alerts that it will send you. If you become upset or distressed as a result of completing the questionnaires, the study doctor will be able to arrange for counselling or other appropriate support. Any counselling or support will be provided by qualified staff who are not members of the research project team. This counselling will be provided free of charge. At the end of the study you will need to return the electronic device to the site.

- Rescue medication: You will be provided with paracetamol, and may take up to 3 grams daily (6 tablets of 500 mg, no more than 2 tablets per intake, at least 4 hours between intakes) for unacceptable pain due to any reason during the study. No other rescue medication can be used during the study. If you cannot tolerate the pain, please call your study doctor.
- Study treatment administration: Detailed training on how to use the study treatment will be provided if you are eligible to participate in the study. The device will record the time and quality of the inhalations you will be taking. Site staff will be reviewing the collected data at each site visit.
- Up-titration (dose starts off low and increases to maintenance dose): During this period, the device will automatically control the dosage, and you will use the study treatment according to the table below:

Day(s)	**Usage**
1	1 time per day (morning or afternoon)
2 and 3	1 time per day (evening)
4 and 5	2 times per day (morning and evening)
6 to end of treatment	3 times per day (morning, afternoon, evening)

- Maintenance Period: You will use the study treatment 3 times per day (morning, afternoon, evening). Inhalations will be possible in intervals of 3 hours or more between the inhalations.
  At home, you will be asked to keep the inhaler at room temperature and charge it if needed with the charger and USB cable supplied by study staff. You will need to bring the inhaler with you to all study site visits so that the study staff could assess your treatment compliance.

The table below shows which procedures and assessments will occur at which visit(s). In addition to the visits described, the study staff may ask you to come in for extra visits, if necessary for your safety.

Study Procedures	**Screening Period**	**Treatment Period (112 days)**																																**Follow-Up Period (28 days)**					**Unscheduled Visit(s)**
		Up-titration Period (27 days)															Maintenance Period (85 days)																						
On Site Visit	1	2	Call	Call	Call	Call	Call	3	Call	Call	Call	4	Call	Call	Call	5	Call	6	Call	7	Call	8	Call	9	Call	10	Call	11 End of Treatment	Call	12	13	Call	14 End of Study	(as needed)
Day	-14 to -1	1	2	3	4	5	6	8	11	13	15	17	19	22	25	28	35	42	49	56	63	70	77	84	91	98	105	112	115	119	126	133	140	
Read and sign informed consent, medical history, demographic data, and height	X																																		
Eligibility to participate	X	X																																	
Urine sample	X	X																												X	X		X	X
Weight and pregnancy test for women who are able to have children	X	X														X				X				X				X					X	X
Vital signs	X	X						X				X				X				X				X				X		X	X		X	X
Full physical examination	X																											X					X	X (may be full or brief)
Brief physical examination		X														X				X				X						X				
ECG	X	X														X				X								X		X			X	X
Blood sample	X	X						X				X				X				X				X				X		X			X	X
PK blood samples		X														X				X				X				X		X				
Spirometry	X	X														X				X								X					X	X

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On Site Visit	1	2	Call	Call	Call	Call	Call	3	Call	Call	Call	4	Call	Call	Call	5	Call	6	Call	7	Call	8	Call	9	Call	10	Call	11 End of Treatment	Call	12	13	Call	14 End of Study	(as needed)
Day	-14 to -1	1	2	3	4	5	6	8	11	13	15	17	19	22	25	28	35	42	49	56	63	70	77	84	91	98	105	112	115	119	126	133	140	
Dispense, return, tracking of rescue medication	X	X						X				X				X		X		X		X		X		X		X		X	X		X	X
Set-up, training, dispensing, and return of eDiary	X																																X	X
Assign the drug you are to take		X																																
Dispense/return inhaler		X																										X						X
Training on inhaler		X																																X
Study team to exchange cartridges								X				X				X		X		X		X		X		X									X
Use the study treatment		Follow up-titration schedule														Use the study treatment 3 times per day																			
Study team will review your eDiary		X						X				X				X		X		X		X		X		X		X		X	X		X	X
Questionnaire(s), questions about how you are feeling, questions about other medicines you are taking	Daily																																	

Caregiver

Your study doctor may decide that a caregiver is necessary to help with your participation in the study. This person should be 18 years or older and be available to contact you as needed, either by phone or in person. The caregiver's role will be to check on you at home for any signs or symptoms of side effects, including changes in your mental state. They may also help with transportation or accompany you to and from study visits if needed.

You will be asked to name your caregiver and to provide their contact details. Your caregiver will be informed about their responsibilities and must provide their consent to the caregiver role.

Costs and Reimbursement

You will be reimbursed $50 via a prepaid [VISA or Mastercard] gift card to cover travel, parking, meals and other expenses associated with attending each of the research project visits onsite. At visits 5 and 11, the reimbursement amount is $250 via a prepaid [VISA or Mastercard] gift card, for attending each of these extended time length visits. Reimbursement will only be paid for visits attended onsite.

There are no additional costs associated with participating in this research project, nor will you be paid. All medication, tests and medical care required as part of the research project will be provided to you free of charge.

4. What do I have to do?

During this study, you will have the following responsibilities:

- Tell your study doctor if you have any allergies, including drug allergies. If you are not sure, ask your family/personal doctor.
- Attend all scheduled visits and become available for phone calls from the study staff.
- Don't take your study medication before a visit to the study site. Bring your eDiary and your Syqe-Fixed dose Inhaler to every site visit.
- Use the study treatment as directed and the inhaler as instructed.
- Return any used and unused study treatments and rescue medication.
- Complete the eDiary as instructed.
- Follow the study doctor's instructions about prescribed medications or over-the-counter medicines that you are taking during this study.
- Tell the study doctor of any changes to your current medications, illnesses or injuries, side effects, or problems that occur during the study.
- Tell the study doctor if you plan to have any surgeries or other medical treatment(s) or procedure(s).
- **You should not perform activities that require mental alertness, judgment, or physical coordination, such as driving or operating machinery, signing legal contracts, or do anything that requires you to be alert while you are taking the study treatment, that is, for the duration of this trial.** You may not drive yourself or operate any other form of transportation (e.g., a bike, scooter, skateboard, etc.) but you may use other forms of transportation to get around (e.g., designated driver, taxi, bus, walk, etc.). Please note you may fail a road side drug test whilst on this study. Despite the legal use of medical cannabis within the context of this study, you should be aware that you could face accusations or misunderstandings related to narcotic substances to which the study treatment belongs. In the event that you should need narcological expertise (this is a specialist who works with people regarding the prevention, treatment, diagnosis and recovery of people with drug-

dependence), please provide the participant identification card and call your study Investigator immediately for support.

- You should continue to make regular visits to your family/personal doctor or any other specialized doctors you were seeing before starting this study because being in the study does not replace regular medical care.
- Make sure that the study treatment is kept out of the reach of children and people who have a limited capacity to read or understand. You are the only person who should use the study treatment.
- Contact the study doctor if you think of any questions about this study after you have already signed this informed consent form.

5. Other Relevant Information about the research project

You will be in this study for approximately 22 weeks, and you will need to come to the study site at least 14 times over this period. It is expected that between 10 and 30 participants will be enrolled at this site.

6. Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with Western Sydney University – NICM Health Research Institute.

7. What are the alternatives to participation

You do not have to take part in this research project to receive treatment at this hospital. Other options are available. Your study doctor will discuss these options with you before you decide whether or not to take part in this research project. You can also discuss the options with your local doctor.

8. What are the possible benefits of taking part?

We cannot guarantee or promise that you will receive any benefits from this research; however, knowledge gained from this research may assist future patients with this condition.

9. What are the possible risks and disadvantages of taking part?

Medical treatments often cause side effects. You may have none, some or all of the effects listed below, and they may be mild, moderate or severe. If you have any of these side effects, or are worried about them, talk with your study doctor. Your study doctor will also be looking out for side effects.

There may be side effects that the researchers do not expect or do not know about and that may be serious. Tell your study doctor immediately about any new or unusual symptoms that you get.

Many side effects go away shortly after treatment ends. However, sometimes side effects can be serious, long lasting, or permanent. If a severe side effect or reaction occurs, your study doctor may need to stop your treatment. Your study doctor will discuss the best way of managing any side effects with you.

Possible risks/side effects associated with the study treatment:

- If you are assigned to use placebo or if the study treatment does not work for you, your diabetic peripheral neuropathic pain symptoms may not improve or may get worse. The study treatment may cause unpleasant side effects or reactions. The most commonly reported side effects in other studies of the study treatment were:
    - euphoric mood,
    - feeling weak,
    - dry mouth,
    - pain,
    - dizziness,
    - restlessness,
    - cough, and
    - fatigue.
- Other possible side effects may include, but are not limited to:
    - nausea,
    - blood pressure changes, including rapid drop in blood pressure when standing up quickly from laying or sitting down (orthostatic hypotension),
    - decreased heart rate,
    - redness and/or dryness of the eyes,
    - unclear speech and slow response time,
    - disorientation,
    - headache,
    - sore throat,
    - sleepiness,
    - palpitations and
    - excessive sweating.
- Increase of appetite and cravings for sweet/fatty food which may lead to increased level of glucose in blood and poorer diabetes control.
- Because the study treatment is investigational, there may be risks and side effects that are unknown. All drugs have a possible risk of an allergic reaction.
- High doses of THC (active ingredient of Syqe Fixed-dose Inhaler) are associated with increased risk of developing substance use disorder. Doses of THC used in this trial are considered relatively low. While risk of developing substance use disorder while using Syqe Fixed-dose Inhaler is low it cannot be completely ruled out.
- Stopping cannabis suddenly can cause cannabis withdrawal symptoms. Common symptoms include feeling anxious, irritable, angry, having trouble sleeping, changes in mood (like feeling sad), and loss of appetite. Most of the time, these symptoms are mild and go away on their own without needing treatment. Although there are no approved treatments for moderate or severe withdrawal symptoms, short-term medications can help with these symptoms if needed.
- Recreational use of cannabis has been reported to increase risk of events related to blood flow to heart and brain such as myocardial infarction and stroke as well as risk of developing changes in heart rhythm.

<u>Managing of possible side effects</u>

To help you manage these side effects, the study team have developed below guidance, which explains the measures you should take at home in the event you experience adverse events.

Please follow these recommendations and contact your study doctor if you need further assistance.

Possible Side Effects	**Measures You Can Take at Home**
Euphoric mood, Restlessness, Disorientation, Poor coordination, Instability	• Find a quiet and comfortable place and have a rest. • Avoid activities that require coordination (e.g., driving or operating heavy machinery). • Contact your study doctor if symptoms persist or worsen.
Somnolence (Sleepiness)	• Take short naps or rest in a dark, quiet and comfortable place. • Avoid activities that require coordination (e.g., driving or operating heavy machinery). • Contact your study doctor if symptoms persist or worsen.
Blood Pressure Changes Symptoms of high blood pressure: - Severe headache - Nosebleeds - Fatigue - Vision problems - Light-headedness - Palpitations - Anxiety Symptoms of low blood pressure: - Light-headedness or dizziness - Feeling sick - Blurred vision - Generally feeling weak - Confusion - Fainting	• For symptoms of low blood pressure, lie down and raise legs. • For symptoms of high blood pressure, rest and avoid stress. • Contact your study doctor if symptoms persist or worsen. • Call emergency service if you experience following symptoms: o Severe chest pain o Confusion and/or blurred vision o Nausea and/or vomiting o Extreme anxiety o Shortness of breath o Seizures
Decreased Heart Rate, Unstable Pulse, Palpitation	• Check your heart rate. • Rest and avoid exertion. • Contact doctor if the heart rate is abnormal (less than 50 beats per minute or more than 120 beats per minute). • If you experience severe or unusual chest pain please call emergency service.

Decrease in Blood Sugar Level A low blood sugar can happen quickly. If not treated right away, low blood sugar can cause a medical emergency. Common causes: Skipping a meal or not eating enough food; taking too much insulin or diabetes pills; more active than usual. Symptoms may include: - Feeling shaky or dizzy - Blurry vision - Feeling weak or tired - Feeling sweaty - Headache - Feeling hungry - Feeling upset or nervous	• Check blood sugar right away if possible. • If it is below your target level, treat for low blood sugar. • If you can't check, treat anyway to be safe. • Treat by eating 3 packets or 1 tablespoon of regular sugar, 4 ounces of regular fruit juice, or 6 ounces of regular (not diet!) soft drink. • Check your blood sugar in 15 minutes. • If it is still low, treat again. • Contact your study doctor if symptoms persist or worsen.
Increase in Blood Sugar Level Keeping your blood sugar under control is important. Too much sugar in your blood, for too long, can cause serious health problems. Common Causes: Too much food, not taking enough insulin or diabetes pills, being less active than normal, stress or illness. Symptoms may include: - Feeling thirsty all the time - Blurry vision - Need to urinate often - Feeling weak or tired - Dry skin - Feeling hungry	• Check blood sugar right away if possible. • Continue to take your diabetes medicine. • Follow your meal plan. • Drink lots of water. • Contact your study doctor if symptoms persist or worsen.
Allergic Reaction Symptoms may include: - Tingling, itching or burning sensation in the mouth - Rapid development of nettle rash - Intense itching - Swelling, particularly of the face - Feeling hot or very chilled - Rising anxiety/feeling scared - Pale or flushed - Abdominal (tummy) pain - Nausea and/or vomiting	• Take an antihistamine. • Let someone know that you are having a reaction and ask them to stay with you to help monitor the reaction to make sure it is getting better, not worse. • Call emergency service if you experience difficulty in breathing - either hoarseness, noisy or wheezy breathing, croupy or choking cough or not being able to talk normally.

If you experience **any concerning side effects**, such as chest pain, difficulty breathing, or severe allergic reactions, call emergency services immediately.

Always reach out to your study physician with any questions or concerns about your symptoms or how to manage them at home.

Possible discomforts and risks associated with the study procedures:

- Blood samples: Taking blood from your arm may cause faintness and/or swelling, pain, redness, bruising, bleeding, or infection (infection rarely happens) at the site where the needle is inserted.
- ECG: Skin irritation is rare but could occur during an ECG from the electrode patches or gel that is used.
- Spirometry: The amount and pattern of breathing required may cause dizziness or fainting.

Pregnancy Risks

The effects of the Syqe fixed dose Inhaler on the unborn child and on the newborn baby are not known. Because of this, it is important that research project participants are not pregnant or breast-feeding and do not become pregnant during the course of the research project. You must not participate in the research if you are pregnant or trying to become pregnant, or breast-feeding. If you are female and child-bearing is a possibility, you will be required to undergo a pregnancy test prior to commencing the research project. If you are male, you should not father a child or donate sperm for at least 1 month after the last dose of study medication.

Both male and female participants must use effective contraception during the course of the research and for a period of 1 month after completion of the research project.

Women

If you are pregnant, planning to become pregnant, or breastfeeding a child, you cannot take part in this study.

Before entering this study, a blood pregnancy test will be done for all women who are able to become pregnant. This test might not detect an early pregnancy. Blood and/or urine pregnancy tests will be repeated during the study.

Female participants who are able to become pregnant must use a highly effective birth control method such as: sexual abstinence for duration of the research study (if it is your lifestyle choice), hormonal contraceptives associated with inhibition of ovulation (pill, patch, injection etc.), intrauterine device (IUD), intrauterine hormone-releasing system (IUS, bilateral tubal occlusion, vasectomised partner.

If you become pregnant during this study or within 9 months after your last dose, you should tell the study doctor as soon as possible. Your use of the study treatment will be stopped, and your involvement in this study will end. You will be asked to sign a separate Information Sheet and Consent Form to provide updates on the progress of the pregnancy and the outcomes until the child is 1 year of age.

Men

Male participants who are not sterile must use a highly effective birth control method such as: vasectomy or sexual abstinence (if it is your lifestyle choice). If your female partner is able to or is planning to become pregnant, you should discuss contraception recommendations with your study doctor.

If your partner becomes pregnant while you are in this study or within 3 months of your last dose, the Sponsor may want to receive updates on the progress of the pregnancy and its outcome. If

your partner agrees to this, she will be asked to sign a separate informed consent form until the child is 1 year of age.

10. What will happen to my test samples?

The blood samples that you give will be sent to a central laboratory, PPD Central Lab Europe in Belgium or Syneos Health Clinique Inc in Canada and used only for the tests specified in the table. You will have the option to allow leftover blood samples to be stored and used for future research, i.e. tests not specified in this informed consent, for up to 25 years after the end of the study. You can provide voluntary consent on a separate form for the use of left-over samples for future research.

The urine samples that you give will be sent to either of the central laboratories listed above and used only for the tests specified in the table and destroyed after the test is completed or at the end of the study.

Your biological samples, including your urine sample and blood sample, will not be given or sold to anyone, nor will they be used for purposes other than the research described in this form. Biological samples will be stored without information that can directly identify you. Your biological samples will not be reasonably identifiable or capable of association with you.

11. What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the research project. If you decide to withdraw, your study doctor will make arrangements for your regular health care to continue. If you decide to continue in the research project, you will be asked to sign an updated consent form.

Also, on receiving new information, your study doctor might consider it to be in your best interests to withdraw you from the research project. If this happens, he/she will explain the reasons and arrange for your regular health care to continue.

12. Can I have other treatments during this research project?

Whilst you are participating in this research project, you may not be able to take some or all of the medications or treatments you have been taking for your condition or for other reasons. It is important to tell your study doctor and the study staff about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell your study doctor about any changes to these during your participation in the research project. Your study doctor should also explain to you which treatments or medications need to be stopped for the time you are involved in the research project.

13. What if I withdraw from this research project?

Taking part in this study is voluntary, and you can leave the study at any time for any reason, and your regular medical care or benefits to which you are entitled will not be impacted.

If a decision is made to stop using the study treatment (but not the study itself), you will be asked to continue your participation in the study (including study visits and procedures).

If you decide to withdraw from the project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing.

If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected by the sponsor up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell them before you join the research project.

14. Could this research be stopped unexpectedly?

This research project may be stopped unexpectedly for a variety of reasons. These may include reasons such as:

• Unacceptable side effects

• The drug/treatment/device being shown not to be effective

• The drug/treatment/device being shown to work and not need further testing

• Decisions made in the commercial interests of the sponsor or by local regulatory/health authorities.

15. What happens when the research project ends?

When you leave the study, you will be under the care of your family/personal doctor, who will decide the best way to treat your diabetic peripheral neuropathic pain. The study treatment will no longer be available to you.

You will be provided with a summary of the results when the research project is completed.

Part 2 How is the research project being conducted?

16. What will happen to information about me?

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal information about you for the research project. Any personal information obtained in connection with this research project that can identify you will remain confidential. Your personal information will only be used for the purpose of this research project, and it will only be disclosed with your permission, except as required by law.

To protect your personal information, the study doctor will replace personal data that can directly identify you (such as your name, address, and telephone number) with a unique code that does not directly identify you. Only your coded information will be sent outside the clinical study location. Personal information that can directly identify you will remain at the clinical study location and your coded information will only be decoded if required by law.

The following information may be used and/or shared:

- Your name, address, contact information, birth date, gender at birth, race, ethnicity, and government identification number;
- Information obtained from your past and current medical history, physical examination and procedures required to determine your eligibility to participate in the study, for example, electrocardiogram (ECG), blood and urine tests, etc.;
- Information that is created or collected from you during your participation in the study, including the dates of treatments and visits, results of the tests above and any other procedures performed during the study;
- Results of questionnaires about your symptoms, including audio responses;

- Information about whether you are sexually active;
- Information about your fertility including whether you are able to have children.

The following individuals and organizations may collect, use, share, or have access to your personal information:

- the Study Doctor, affiliated doctors, health care providers, and staff;
- Ethics Committees, the Therapeutic Goods Administration (TGA) or other government bodies as necessary around the world;
- the Sponsor and its representatives, its business collaborators, monitors, auditors, vendors, laboratories, clinical research organization; and
- if required, your personal doctor, to collect additional medical information.

Personal information about you may be obtained from your health records held at this and other health services for the purpose of this research. By signing the consent form you agree to the study team accessing health records if they are relevant to your participation in this research project.

Your health records and any information obtained during the research project are subject to inspection (for the purpose of verifying the procedures and the data) by the relevant authorities and authorized representatives of the Sponsor, Syqe Medical Ltd and in Australia Syneos Health Australia Pty Ltd, the institution relevant to this Participant Information Sheet, Western Sydney University – NICM Health Research Institute, or as required by law.

Your personal information may be transferred to parties in countries (and regions) other than Australia, including the US and Europe for review by the organizations listed above. Syneos Health Australia Pty Ltd and the Sponsor will comply with all local data protection laws to protect your personal information, even in countries whose data protection laws are less strict than those of this country. In all cases, when dealing with your personal information, Sponsor and its agents will comply with the Australian Privacy Act of 1988 and the privacy laws of NSW. If you have any concerns on how your information is handled, please feel free to ask a member of the study team for more information.

Your personal information will be retained for 25 years or longer, as necessary for the purposes described in this form.

By signing the consent form, you authorize release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in a way that you cannot be directly identified, except with your permission. Information about your participation in this research project may be recorded in your health records.

In accordance with relevant Australian and/or NSW privacy and other relevant laws, you have the right to request access to your information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your information.

17. Complaints and compensation

If you are injured as a result of your participation in this trial, you may be entitled to compensation. There are two avenues that may be available to you to seek compensation.

1) Sponsors of clinical trials in Australia have agreed that the guidelines developed by their industry body, Medicines Australia, will govern the way in which compensation claims from injured participants are managed by sponsors.

However, as guidelines, they do NOT in any way dictate the pathway you should follow to seek compensation. The sponsor is obliged to follow these guidelines.

These guidelines are available for your inspection on the Medicines Australia Website (www.medicinesaustralia.com.au) under Policy – Clinical Trials – Indemnity and Compensation Guidelines. Alternatively, your study doctor can provide you with a hard-copy of the guidelines.

2) You may be able to seek compensation through the courts.

It is the recommendation of the independent ethics committee responsible for the review of this trial that you seek independent legal advice before taking any steps towards compensation for injury.

18. Who is organizing and funding the research?

This research project is being conducted by Syqe Medical Ltd and sponsored in Australia by Syneos Health Australia Pty Ltd.

Syqe Medical Ltd may benefit financially from this research project if, for example, the project assists Syqe Medical Ltd to obtain approval for a new treatment.

By taking part in this research project you agree that samples of your blood or tissue (or data generated from analysis of these materials) may be provided to Syqe Medical Ltd. Syqe Medical Ltd may directly or indirectly benefit financially from your samples or from knowledge gained through analysis of your samples.

You will not benefit financially from your involvement in the research project even if, for example, your samples (or knowledge acquired from analysis of your samples) prove to be of commercial value to Syqe Medical Ltd.

In addition, if knowledge acquired through this research leads to discoveries that are of commercial value to Syqe Medical Ltd, the study doctors or their institutions, there will be no financial benefit to you or your family from these discoveries.

Western Sydney University – NICM Health Research Institute will receive a payment from Syneos Health Australia Pty Ltd for undertaking this research project. Dr Orit Holtzman Assif (the study doctor) has previously engaged in consulting services for Syqe on a casual basis, outside this current research project. Dr Holtzman will sit on a panel as part of this research project which will include; review and provide opinion on draft trial documents that relate to participant recruitment and retention material; provide opinion on the recruitment and retention of participants in Australia and participate in a Global Investigator Panel (GIP) meeting; engage during the meeting to help identify potential barriers to recruitment. Dr Holtzman Assif will be paid for this. Dr Holtzman Assif has not and will not have any other financial or other personal benefits from her involvement in this research project.

No member of the research team will receive a personal financial benefit from your involvement in this research project (other than their ordinary wages).

19. Who has reviewed the research project?

The Bellberry Human Research Ethics Committee has reviewed and approved this study in accordance with the National Statement on Ethical Conduct in Human Research (2007 – incorporating all updates). This Statement has been developed to protect the interests of people

who agree to participate in human research studies. Should you wish to discuss the study or view a copy of the Complaint procedure with someone not directly involved, particularly in relation to matters concerning policies, information or complaints about the conduct of the study or your rights as a participant, you may contact the Operations Manager, Bellberry Limited on 08 8361 3222.

20. Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the principal study doctor on (02) 8529 0926 or any of the following people:

Clinical contact person

Name	Dr. Orit Holtzman Assif
Position	Principal Investigator
Telephone	0421381731
Email	dpnpstudy@westernsydney.edu.au

For matters relating to research at the site at which you are participating, the details of the local site complaints person are:

Complaints contact person

Name	Mike Armour
Position	Director of Research – Western Sydney University
Telephone	0402541526
Email	dpnpstudy@westernsydney.edu.au

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC approving this research and HREC Executive Officer details

Reviewing HREC name	Bellberry Ltd
HREC Executive Officer	Operations Manager
Telephone	08 8361 3222
Email	bellberry@bellberry.com.au

Consent Form - *Adult providing own consent*

Title	A Double-blind, Randomized, Placebo-controlled, 4-arm Parallel-group, Multiple-Dose Study to Assess Efficacy and Safety of Medical Cannabis Aerosol via the Fixed-dose Syqe Inhaler as an Add-on Treatment of Diabetic Peripheral Neuropathic Pain.
Protocol Number	Syqe-004
Global Project Sponsor	Syqe Medical Ltd.
Local Project Sponsor	Syneos Health Australia Pty Ltd.
Principal Investigator	Dr. Orit Holtzman Assif
Associate Investigator(s) *(if required by institution)*	
Location *(where PI will recruit)*	Western Sydney University – NICM Health Research Institute. 158 Hawkesbury Road, Westmead, NSW, 2145

Declaration by Participant

- I have read the Participant Information Sheet or someone has read it to me in a language that I understand.
- I am 18 years of age or over.
- I have been given the chance to ask any questions that I had about the study, and all questions that I asked were answered to my satisfaction.
- I understand the risks of taking part in this study as described in this informed consent form.
- I freely consent to be treated with the study treatment under the study doctor's care. I understand that there is no guarantee that I will receive any benefits from taking part in this study. By voluntarily consenting to participate I will follow the study doctor's instructions.
- I understand that I am free to withdraw from the study at any time for any reason. I will tell the study doctor if I decide to withdraw so that my participation may end in an orderly manner and my future care can be discussed. I understand that my study doctor can stop my participation in the study at any time. Withdrawing from participation at any time will not cause any penalty or consequences to my quality or standard of care.
- I understand that I will be told of any new information that might relate to my willingness to continue in the study.
- I understand that relevant personal data may be used for the purpose of this clinical investigation. The Sponsor's representatives, local regulatory authorities, and EC/IRB representatives may be granted direct access to my medical records.
- I understand that I cannot participate in another research study while taking part in this study.
- I consent to my general practitioner being informed of my participation in this study and of any clinically relevant information noted by the study doctor in the conduct of the trial.
- I understand that I will receive a signed and dated copy of this informed consent form for my records.

- **I agree to name a caregiver, as mandated by the study doctor.**
  □ Yes □ No □ Not mandated / Required

Name of Participant (please print) _____
Signature _____ Date _____

Under certain circumstances (see Note for Guidance on Good Clinical Practice CPMP/ICH/135/95 at 4.8.9*) a witness* to informed consent is required.*

Name of Witness* to Participant's Signature (please print) _____
Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/ Senior Researcher† (please print) _____
Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

Form for Withdrawal of Participation – Adult providing own consent

Title	A Double-blind, Randomized, Placebo-controlled, 4-arm Parallel-group, Multiple-Dose Study to Assess Efficacy and Safety of Medical Cannabis Aerosol via the Fixed-dose Syqe Inhaler as an Add-on Treatment of Diabetic Peripheral Neuropathic Pain.
Protocol Number	Syqe-004
Global Project Sponsor **Local Project Sponsor**	Syqe Medical Ltd. Syneos Health Australia Pty Ltd.
Principal Investigator	Dr. Orit Holtzman Assif
Associate Investigator(s) *(if required by institution)*	
Location *(where PI will recruit)*	Western Sydney University – NICM Health Research Institute. 158 Hawkesbury Road, Westmead, NSW, 2145

Declaration by Participant

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with Western Sydney University – NICM Health Research Institute.

Name of Participant (please print) _____

Signature _____ Date _____

In the event that the participant's decision to withdraw is communicated verbally, the Study Doctor/Senior Researcher will need to provide a description of the circumstances below.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the participant has understood that explanation.

Name of Study Doctor/ Senior Researcher† (please print)	
Signature	Date

† A senior member of the research team must provide the explanation of and information concerning withdrawal from the research project.

Note: All parties signing the consent section must date their own signature.