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Re:Cognition Health
COMPLETE COGNITIVE CARE

Patient Information sheet and informed consent form

Study title: A Phase 3, 4-week, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Study of TD-9855 in Treating Symptomatic Neurogenic Orthostatic Hypotension in Subjects With Primary Autonomic Failure

Study protocol: 0169

Study drug: TD-9855, referred throughout the document as the "study drug"

Sponsor of the study: Theravance Biopharma Ireland Limited, Connaught House, 1 Burlington Road, Dublin 4, D04 C5Y6, Ireland

Investigator: **Dr Emer MacSweeney**

Patient Name: _____

Patient Number: _____

Introduction

You are invited to take part in a clinical research study. To help you decide, you should understand the study and what it will involve for you. To make an informed decision to take part – you should know the purpose of the study, the procedures, the benefits and risks of the study, the discomforts and the precautions taken. This process is called 'informed consent'. Please take the time to read the following information carefully and discuss it with others. Please ask your study doctor if there is anything that is not clear or if you would like more information.

It cannot be promised that the study will help you but the information we get from this study may help improve the future treatment of people with the same condition.

Once you have decided that you want to take part, you will be asked to sign the informed consent form. You will be given a copy of the signed form to keep, and the original will stay at the study centre.

You will not be allowed to participate in the study unless the informed consent form is signed.

Around 188 patients in approximately 100 study centres around the world will take part in this study.

What is the purpose of the study?

A clinical research study is a medical study that helps to answer important questions about whether an investigational drug works and how safe it is. Investigational means that it is has not yet been approved for use outside of research studies like this one. This study will look at whether an investigational drug called TD-9855 works and how safe it is for treating symptomatic neurogenic orthostatic hypotension (snOH), (explained below) in people with Parkinson's disease (PD), multiple system atrophy (MSA) or pure autonomic failure (PAF). It will also look at the effects of TD-9855 on your general wellbeing. If applicable, if the person who cares for you (your 'caregiver') signs a separate consent form, the study will also collect information on his/her experiences of caring for you. TD-9855 will be referred to throughout the rest of the document as the 'study drug'.

This is a Phase 3 study. This means that the study drug has already been given to a smaller group of people in other clinical research studies with your condition and other types of conditions including people with attention-deficit hyperactivity disorder (ADHD) and fibromyalgia. In this study, it will be tested in a larger group of people with snOH and PD, MSA, or PAF.

What is symptomatic neurogenic orthostatic hypotension?

If someone has orthostatic hypotension (OH), it means that they get low blood pressure when they stand up. If someone has neurogenic OH (nOH), it means that the OH is caused because a part of the nervous system called the autonomic nervous system is not working properly. Your autonomic nervous system is responsible for important body functions, such as controlling your heart rate and blood pressure. nOH can occur in people who have a condition that affects the autonomic nervous system, such as PD, MSA, or PAF. If someone has symptomatic nOH (snOH), it means that they are experiencing symptoms of nOH, such as dizziness, feeling lightheaded, feeling faint, or feeling like they might black out.

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What medication is being tested?
The study drug is called TD-9855. It is an investigational study drug that is being developed for a range of medical treatments, including for snOH.

In people with nOH due to PD, MSA, or PAF, nerve cells do not release enough norepinephrine (also called noradrenaline) (a chemical that is used by cells to communicate with one another). Normally when we stand up, nerve cells controlling our blood pressure release norepinephrine, which acts on receptors in the walls of blood vessels and in the heart to keep our blood pressure up and stop it from dropping. In conditions such as PD, MSA and PAF, these nerve cells are damaged, which means that there is not enough norepinephrine released to work properly. Normally, once norepinephrine has worked on the receptors it is either broken down by the body or taken back up into nerve cells to be 'recycled'. The study drug has been designed to prevent norepinephrine from being taken back up by nerve cells, thereby increasing the amount of norepinephrine available. It is hoped that this might reduce the symptoms of nOH.

People taking part in the study will either receive the study drug or a dummy drug (placebo).

The study drug will be compared with a placebo, which looks the same as the study drug but does not contain any active ingredients. A placebo is used to check that any effects seen in people taking part in the study are because of the study drug itself, and not because the person thinks they are taking the study drug. Study drug and placebo are collectively referred to throughout the rest of the document as the 'study medication". If you agree to take part and the study is right for you, you will be randomly assigned (by chance – like tossing a coin) and will have a 50/50 chance of receiving either the study drug (10 mg per day) OR placebo. You will take a single tablet of the study medication (study drug or placebo) by mouth at the same time each morning with a glass of water. The study medication can be taken with or without food.

This study is 'double-blinded', which means that neither you nor your study team will know which study medication you are taking. However, the study doctor can find out which study medication you are taking if doing so is considered necessary for your safety.

Why have I been invited?
You are being asked to take part because you:

- are at least 30 years of age
- have snOH
- have either PD, MSA, or PAF.

Do I have to take part?
Taking part in this study is voluntary – you do not have to take part to be treated for your condition. If you decide not to take part in this study, it will not affect your ability to receive medical care. You can stop taking part in the study at any time without giving any reason. This will not affect your future treatment or your relationship with your study team.

What will happen to me during the study?

Before you take part in the study
You will have the time and the chance to ask any questions that you may have before signing the informed consent form. If you agree to take part, you will be in the study for up to 8 weeks. During this time, you will attend 7 study visits in total. You will be asked not to make any significant changes to your diet while taking part in the study, and to drink plenty of water during study visits. This clinical research study is split into a screening period, treatment period, and a follow-up period.

Screening period
The screening period will last for up to **2 weeks** and will involve at least **1 visit** to the study centre.

During the screening period, the study doctor will perform tests and assessments to check that this clinical research study is right for you. You will also receive training to help you better recognise the symptoms of nOH, to help you to answer some questionnaires used in the study. You will receive regular refresher training throughout the study.

Once the screening period has finished, you will enter the treatment period.

Treatment period

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The treatment period will last for **4 weeks** and will involve **5 visits** to the study centre (about 1 visit per week) for tests and assessments.

At your first treatment period visit, the study doctor will check that the study is still right for you. You will also be given a Dosing Diary, a Blood Pressure and Position Diary, and an Incidence of Falls Diary (patient diaries are described later in this document). If the study is still right for you, you will take your first dose of study medication the next morning.

For the rest of the treatment period, you will take the study medication every morning at home as instructed and continue to attend study centre visits. Once the treatment period has finished, you will enter the follow-up period.

If you choose to leave the study early, you will also be asked to attend an early termination visit, which will involve the same tests and assessments as the last treatment period visit.

While you are in the study, there are some medications that you are not allowed to take. For more information, please view the "**What will I have to do?**" section of this document. During the study, you may also be given midodrine (at the discretion of the study doctor) to help manage snOH.

Follow-up period

The purpose of the follow-up period is to check your health once you have finished receiving the study medication. This part of the study will involve **1 visit**, which will take place **2 weeks** after your last dose of the study medication (even if you choose to leave the study early). If you complete the 4-week treatment part of this study, you may be able to continue in another study called Study 0170. If you take part in Study 0170, you will not have the follow-up visit.

The tests and assessments that you can expect during the screening, treatment, and follow-up periods of the study are shown in Table 1 below. A description of each test and assessment you can expect to receive is detailed after Table 1.

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Table 1. Tests and assessments

Assessments	Screening period	Treatment period					Follow-up period
	Day -14 to -7	Day 1	Day 8	Day 15	Day 22	Day 29	Day 43
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Sign Informed Consent Form	X						
Check the study is right for you	X	X					
Height measurement	X						
Weight measurement	X	X	X	X	X	X	X
Physical and neurological examinations	X	X				X	
Vital signs (blood pressure, heart rate, breathing rate and body temperature)	X	X	X	X	X	X	X
Electrocardiogram (ECG)	X					X	
24-hour blood pressure monitoring		X	X		X		
Tilt table test	X	X					
Standing test	X	X	X	X	X	X	
Valsalva Maneuver (only if you have PAF)	X						
Pregnancy test (for women of child bearing potential only)	X	X				X	
Blood tests	X	X	X	X		X	X
Urine tests	X	X		X		X	
Take study medication at home		←	—	—	—	→	
Return unused study medication and/or receive new study medication		X	X	X	X	X	

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	Day -14 to -7	Day 1	Day 8	Day 15	Day 22	Day 29	Day 43
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Return old Diaries and/or receive new Diaries (Dosing Diary, a Blood Pressure and Position Diary, and an Incidence of Falls Diary)	X	X	X	X	X	X	
Questionnaires	X	X	X	X	X	X	X
Report any side effects you are experiencing	X	X	X	X	X	X	X
Report any other medications you are taking	X	X	X	X	X	X	X
Medical History (including smoking history)	X						

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Physical and neurological examinations: At your first study visit, the study doctor will look at your general appearance, limbs, head, ears, eyes, nose, and throat, neck, skin, heart, and blood circulation, lungs, abdomen, lymph nodes, and nervous system (reflexes, balance, coordination, movement, senses, and strength).

Vital signs: This will involve measuring your heart rate, blood pressure, breathing rate, and body temperature.

Electrocardiogram (ECG): This is a test during which sticky pads are placed on your chest. An electrical measurement of your heartbeat and heart rhythm will be taken to check the health of your heart.

24-hour blood pressure monitoring: Between Visit 1 (screening) and Visit 2, you will be provided with special blood pressure monitoring equipment. You will need to wear it for 24 hours before Visit 2 (Day 1), Visit 3 (Day 8), and Visit 5 (Day 22) to record your blood pressure. The recording should be started within 3 days before each of these visits. Readings will be taken automatically every 2 hours, beginning on the hour. You will need to write down (in the Blood Pressure and Position Diary) the day of the week and the start date of each 24-hour blood pressure monitoring session. For each reading, you will also need to write down (in the same paper diary) the time of the reading, your body position, and any comments you might have. The study doctor will explain this to you in more detail.

Tilt table test: This test will trigger the symptoms of nOH (e.g. dizziness, feeling lightheaded, feeling faint, or feeling like you might black out). The purpose of the test is to check that the study is right for you, and to help you better recognise the symptoms of nOH. You will lie down flat on a table, with straps to hold you in place, and be asked not to move for approximately 25 minutes. The table will be tilted upwards by more than or equal to 60 degrees and your blood pressure and heart rate will be measured. During this time, you will be observed by the study doctor and may be observed by at least one representative of the sponsor that is hired to assist the research team with this test. The tilt table test will be done during Visit 1 (screening) and Visit 2 (Day 1) and will be done at least 2 hours after your last meal.

Standing test: You will be asked to alternate between 10 minutes of sitting and 10 minutes of standing for about 30 minutes. During this time, your blood pressure and heart rate will be monitored.

Valsalva Maneuver: This will only be done for people with PAF. It is a breathing technique that can be used to help diagnose a problem with the autonomic nervous system a symptom of snOH. You will be asked to hold your nose, close your mouth, and attempt to exhale (like you are blowing up a balloon).

Blood tests: Blood samples will be taken during the study. These samples will be used for some, or all, of the following reasons:

- To look at the levels of various chemicals in your blood (sodium, potassium, calcium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, total protein, albumin, alkaline phosphatase, ALT, AST, bilirubin, lactate dehydrogenase, and creatine phosphokinase)
- To check how well your liver and kidneys are working
- To check how well your blood clots
- To check the different types of cells in your blood
- To see how much of the study drug is in your blood, how it is processed and what the body does with it (called ‘pharmacokinetics’)
- To see what the study drug is doing to your body (called ‘pharmacodynamics’)
- To look at the amount of norepinephrine released in the body.

The total amount of blood that will be taken during the study is up to 110 milliliters (mL) or just under 7.5 tablespoons. In some cases, blood tests may need to be repeated and additional blood samples may be needed for safety follow-up.

Urine tests: You will be asked to provide a urine sample in the clinic, which will be used to check your general health, such as how well your liver and kidneys are working.

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Pregnancy test: This is only for women who are able to have children. You will have a urine pregnancy test. If the result is positive, you may have a blood pregnancy test to confirm that you are pregnant.

Patient diaries: You will be given a booklet that contains a Dosing Diary where you will be asked to record the date and time that you take the study medication. The booklet also contains an a Falls Diary, to record any falls that you might have during the study, and a Blood Pressure and Position Diary to record your body position at the time of blood pressure measurements by the automated blood pressure reading device.

Questions and questionnaires: At your first visit, you will be asked questions about the following: your age, sex, race, ethnicity, medical history, smoking history, past and current medications. At every other visit, you will be asked questions about your health and any medications you have taken since the last study visit. Questionnaires will be completed on an electronic device.

You will also regularly complete questionnaires throughout the study, which will be about the following:

- Your general well-being
- Your emotional well-being
- Your memory and thinking
- How snOH affects you in your daily life
- Whether your snOH is getting better or worse.

If you have PD or MSA, you will be asked to complete additional questionnaires about your PD or MSA symptoms.

The study will also collect information on the experiences of the person caring for you. If applicable, the person who cares for you (your 'caregiver') will be asked to complete a questionnaire about how caring for you affects their life. Your caregiver will need to read a separate information sheet and sign a consent form. Your participation in the study will not be affected if the caregiver does not consent to completing the questionnaire.

Expenses and payment

You will be provided with all study medication, examinations and medical care related to the study. All reasonable travel and other expenses incurred as a result of taking part in the study will be reimbursed. You will also be paid a stipend (a payment) for your taking part in this study. If you agree to take part in this research study, you will receive £66 per completed study visit for your time and effort and to cover for any refreshments for you and your caregiver. The study doctor will explain this to you in more detail.

What will I have to do?

- You will have to go to the study visits, follow the instructions the doctors and their team give you and take the study medication as directed.
- Please tell the study team if you think that you will not be able to attend a study visit so that it can be rescheduled.
- You must provide accurate and complete information about your medical history and your present condition.
- You must tell the study team about any new symptoms that you experience during the study. If you notice any changes in your health, please contact the study team as soon as possible.
- Please also inform your study team as soon as possible if you are hospitalised for any reason.
- You must tell the study team about any medications (including vaccinations, herbal medications, homeopathic medications, vitamins, supplements, and over-the-counter medications) that you are taking. You should also check with the study team before taking any new medications.
- There are medications which you will need to avoid while taking part in the study. Your study doctor will help facilitate what medications are appropriate for you with other healthcare professionals looking after you while you are in this study.
- All unused study medication and the used packaging must be returned to the study centre at every visit after enrollment on Day 1.

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- You must complete your patient diaries as instructed.
- You must return the patient diaries, and your 24-hour blood pressure monitoring equipment, to the study centre at your next visit.
- Please do not make any significant changes to your diet while taking part in the study. Please also remember to stay hydrated during study visits.
- If you are a smoker, it is recommended that you either:
  - stop smoking more than 7 days before your first dose of study medication, OR
  - not make any changes to the amount you smoke while taking part in the study.
- If you are a woman who is able to have children, or a man with a female partner who is able to have children, you must agree to follow the study's birth control requirements. For more information, please view the "Harm to the unborn child" section of this document.
- If you or your partner becomes pregnant during the study, you must stop taking the study medication and inform the study doctor immediately.
- You must not take part in any other studies involving an investigational medicinal drug while you are taking part in this study.

What will happen to any samples I give?

As part of this study, we will obtain blood and urine samples from you. They will be sent to a qualified laboratory for analysis. They will only be used for tests listed in this consent form. The urine and blood samples will be used to check your general health, such as how well your liver and kidneys are working, the different types of cells in your blood, and how well your blood clots. Samples will also be used for pregnancy testing, to measure the amount of norepinephrine released in your body, and to look at the pharmacokinetics and pharmacodynamics of the study drug.

Blood and urine samples will be shipped outside of the United Kingdom and will be stored and analysed in a secure facility at a designated location in Ireland and the United States during the study. At the end of the study, all unused samples will be shipped and stored in a secure facility in the United States for up to 5 years after the study has ended. The storage of 5 years is to allow for any retesting that may be required. Your name will not appear on the samples or on data obtained from the analysis of your samples. Rather, your samples and data will be identified by your study patient number only.

If you withdraw your consent from participating further in the study and samples have already been taken from you, you may request that your samples be destroyed, and no new data generated from your samples. However, data already collected cannot be removed.

For carrying out any new analysis on the samples not connected to this study, your permission will be required – you would be asked to sign a new consent form to allow further use of the samples. You have the right to refuse if you do not want your samples to be further analysed.

The sponsor reserves the right to destroy your sample(s) for any reason during the storage period without further notice.

What alternative treatments are available?

Taking part in this study is voluntary – you do not have to take part to be treated for your condition. Your study doctor will discuss with you any other treatments or investigational drugs or treatments that may be available, and will also discuss their risks and benefits. If you decide not to take part in this study, it will not affect your ability to receive medical care.

What could be the side effects of the study drug?

As with all medications, the study drug may cause some side effects. Every person's reaction to a new medication can be different. You may experience some or none of the side effects listed below, or you could experience new side effects that are not known at this time.

Approximately 450 people have taken the study drug in the two completed studies in patients with ADHD and fibromyalgia. Based on the results of these studies, side effects that are considered related to the study drug are: palpitations (feeling like your heart is beating too hard or too fast) (1.6%), postural orthostatic tachycardia syndrome (your heart rate increases when you stand up after lying down) (1.6%), tachycardia (unusually fast heartbeat) (2.7%), constipation (4.4%), diarrhoea (2%), dry mouth (5.3%), nausea (5.3%), fatigue (feeling generally tired) (6%), decreased appetite (6.9%), dizziness

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(including when changing your posture) (10.6%), headache (10.4%) and insomnia (trouble sleeping) (4.7%).

Initial results from of an ongoing study involving 21 patients with snOH due to PD, MSA, or PAF showed 6 patients had side effects that were considered related to the study drug. These side effects, which were not experienced in all 6 patients, were vomiting, swelling of the lower legs or hands, reddening of the skin, headache, fainting, flushing (reddening of the face), and high blood pressure.

If during the study you experience a side effect of any kind, please tell your study team as soon as possible (see 'Who should I contact for more information?').

Any side effects or other health issues occurring during the study will be followed up by the study doctor until it is resolved.

A special committee (group of people), called an 'independent data monitoring committee', will evaluate and monitor all reported symptoms or adverse reactions throughout the study. Based on this safety data, the committee members will make recommendations about whether anything in the design of the study needs to change and whether it is safe for the study to continue.

What could be the side effects of midodrine?

In the event that you experience any worsening in your snOH during the study where you require the use of another medication to control it the study doctor may suggest the use of midodrine. Midodrine is a drug that is approved to treat severe OH in the UK. It works by raising your blood pressure.' It is normally taken 3 times a day. As with any medicines you may experience side effects. The most frequent side effects reported with midodrine are: lying and sitting hypertension (high blood pressure) paresthesia (pins and needles), itching (mainly of the scalp), goosebumps, chills, skin rash and redness, heartburn, nausea, inflammation of the mouth and lips, the urge to urinate, urine retention, and/or a change in frequency. You may, however, experience other side effects not listed here. Your study doctor can provide further information relating to these side effects.
You should inform your study team immediately if you think you are experiencing any of these or if you have any change in your health.

What are the possible disadvantages or risks of taking part?
It is possible that the symptoms of your condition will not improve during the study or may even worsen. Treatment with this study drug may also involve risks to your future health that we currently don't know about.

Possible risks of study procedures

Blood samples: You may experience some discomfort when blood samples are taken, such as pain at the site where the blood has been drawn, bruising, occasional light-headedness and, rarely, fainting.

ECG: When you have an ECG, small sticky pads are applied to certain parts of your body (chest, wrists and ankles). Some areas on which the patches are placed may need to be shaved. You may also feel a small amount of irritation on the skin after these pads are removed.

Tilt table test: You may experience changes to your blood pressure and/or heart rate, dizziness, fainting, headache, and feeling unwell.

Valsalva maneuver: You should not use this maneuver if you have a high risk of heart attack or stroke. You should tell the study doctor about any heart problems you may have and your study doctor will advise you if you can use this maneuver.

Harm to the unborn child

For men and women: Currently we are not fully aware of the effects of the study drug on unborn babies, or on pregnant or breastfeeding women. The study drug may lead to new, previously unknown, side effects and this may involve risks to you or your/your partner's unborn baby. Therefore, pregnant or breastfeeding women are not allowed to participate in this study. Women who are able to have children will be asked to take a pregnancy test at the start of the study. If you are a male, you should not father a child or donate sperm.

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You must be using a highly effective form of birth control while you are taking part in the study. You must also agree to continue to use a highly effective form of birth control for 30 days after you stop taking the study medication. Highly effective birth control may include implants, injectables, combined oral contraceptives, some intrauterine devices (IUDs), sexual abstinence, or a vasectomised or sterilised partner. You should discuss methods of effective contraception with your study doctor.

For women: If you become pregnant after you start taking the study medication or within 30 days of you stopping taking the study medication, you must stop taking the study medication and tell the study doctor immediately. You will need to have an end-of-study visit to check your health. The study doctor will also ask to follow you and your baby's health during the pregnancy and after your baby is born.

For men:

If your partner becomes pregnant after you start taking the study medication or within 30 days of you stopping taking the study medication, you should report the pregnancy to the study doctor immediately. Your partner will be asked to sign a separate consent form to allow the study doctor to follow her and the baby's health until after the baby is born.

What are the possible benefits of taking part in this study?
If you decide to take part in this research study, there is no guarantee there will be any benefit to you. You might receive placebo during the study. Even if you receive the study drug, your snOH may stay the same, improve, or become worse. There may or may not be a direct benefit for you now, but information from this study may help us to treat people with snOH better in the future.

The sponsor company and the sponsor's group affiliates have an economic interest in developing new drugs and medical tests. The results and data collected from this study, including your personal data, may lead to the development of commercial products for the diagnosis, cure, mitigation, treatment, or prevention of disease. Research resulting from the use of your personal data which is collected in this study may result in discoveries and inventions, some of which may be patentable, and the sale of products and services. You will not receive any compensation in the event that a commercial product or service results from research using your personal data.

What happens when the research study stops?
During the study you will receive the study medication or treatment free of charge. The study drug will not be available as a prescription immediately after the end of the study. There is no guarantee that you will continue to receive this particular drug when you have finished taking part in the study, even if the drug is beneficial to you. The care you receive after the study has ended may involve a different drug or treatment, which your usual clinical team considers to be the most suitable alternative.

Your participation in the study may end at any time due to (but not limited to) the following reasons:

- You decide to withdraw.
- Your study doctor or the sponsor decides you should be withdrawn, because, for example:
  - you need to be treated with a medication that is not allowed during the study
  - there is a safety concern and it is in your best interest to withdraw
  - you do not follow the study instructions (e.g. missed visits, missed doses of study medication)
  - there are changes in your health or condition which make you ineligible for continued participation in the study
- You become pregnant (if you are a woman who is able to have children) or decide that you want to become pregnant during the study.
- The sponsor decides to suspend or terminate the study.

If you have a reaction to the study drug, your participation may be stopped at any time by the study doctor or sponsor without your consent.

If the study is stopped, you will be told, and your study doctor will make arrangements for continuation of your care with your usual clinical team. The expenses for continued care after your participation is stopped or the study is stopped will not be covered by the study sponsor (except for compensation for study related injury as described below.)

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If you complete the 4-week treatment part of this study (Study 0169), you may be able to continue receiving study medication in another study, called Study 0170.

What if I have a question?
If you suffer a serious illness or injury during this study, please seek emergency care and ensure the study team is informed..

If you have a question, concern or complaint about any part of this study, you should ask to speak to the study doctor or a member of the research team, who will do their best to help (see 'Who should I contact for more information?').

If you have any questions about your rights as part of the research, or any concerns or complaints about the research that you do not want to discuss with the study doctor or research team, see 'Who should I contact for more information?'.

Compensation for study related injury
Any compensation payable for any injury caused to you by taking part in this study will be in line with applicable law and the guidelines of the Association of the British Pharmaceutical Industry (ABPI). The sponsor will pay for the cost of medical treatment for any injury that is directly due to treatment with the study drug or study procedure (that has been used as described in the study protocol). The sponsor will not compensate you where the injury has happened because a procedure has been carried out that is not in line with the study protocol or where the study doctor has acted negligently.

The sponsor has taken out an insurance policy to cover compensation for any personal injury resulting from your taking the study drug, provided such personal injury is not due to fault or negligence of the study doctor or his team.

If you have private medical insurance, please check with your insurance company that taking part in this study will not affect your policy.

Withdrawing from the study will not prevent you from receiving compensation for a study related injury which occurred while you were taking part in the study. Signing this form does not result in you losing any of your legal rights to seek compensation for negligence which results in injury to you. This is true regardless of whether the negligent party is the sponsor, the study doctor, the site where the study occurs, or someone else.

What if new information about the study drug becomes available?
Sometimes new information about the study drug is received. You will be told if any relevant new information becomes available that may affect your willingness to carry on taking part in the study. If this happens, your study doctor will contact you as soon as possible, and will discuss whether you should continue in the study. If you decide not to carry on, your study doctor will ensure your usual clinical team is informed. If you decide to continue in the study, you may be asked to sign a new consent form.

Also, if new information becomes available, your study doctor may stop your participation without your consent. If this happens the reasons will be explained, and arrangements made for your care to continue.

What will happen if I don't want to carry on with the study?
You can stop taking part in the study at any time without giving any reason. This will not affect your future treatment or your relationship with your study doctor. If you stop taking part, please tell your study team immediately. You will be asked to return to the study centre for an end-of-study assessment, and to return your patient diaries, all unused study medication, and your 24-hour blood pressure monitoring equipment. You may also be asked for permission to be contacted at a later date by your study team to collect additional data about your condition for this study .

Will my taking part in this study be kept confidential and how will my personal information be used?
Theravance Biopharma Ireland Limited is the sponsor for this study based in the Republic of Ireland. We will be using information from you and your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. Theravance Biopharma will keep identifiable information about you for 25 years after the study has finished.

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Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that it has already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible. You can find out more about how we use your information by contacting your study doctor.

The study site will collect information from you and your medical records for this research study in accordance with our instructions.

The study site will keep your name, NHS number and contact details confidential and will not pass this information to the sponsor, Theravance Biopharma Ireland Limited. The study site will use this information as needed, to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Certain individuals from the sponsor, Theravance Biopharma Ireland Limited and regulatory organisations may look at your medical and research records to check the accuracy of the research study. The Sponsor, Theravance Biopharma Ireland Limited will only receive information without any identifying information. The people who analyse the information will not be able to identify you and will not be able to find out your name, [NHS number] or contact details.

The study site will keep identifiable information about you from this study for 25 years after the study has finished.

Theravance Biopharma Ireland Limited will act as the data controller for this study. On behalf of the Sponsor, the study doctor and research team will collect, record and use personal information about you for the study purposes. Your personal information collected during the study may include sensitive information about your physical or mental health or condition, and health information about you in medical records, and other personal information such as your name, address, telephone number, race/ethnicity, date of birth and gender. Your privacy and your personal information will be protected using measures which follow the requirements applicable in the United Kingdom for the protection of your personal information. Any information about you that is collected during this study will remain confidential.

During the study, your collected personal information including your medical files may be disclosed to the Sponsor, its representatives assisting with the study research, including the central laboratory, study monitors, and to auditors, government or regulatory health authorities. Your medical files will be reviewed only at the hospital (or study doctor's office) in order to check the information and verify the clinical study procedures, without breaking your confidentiality.

All information which is collected about you in records that leave the study centre for the purposes of medical, laboratory, statistical or regulatory activities related to the study research will be identified by your study patient number. Your name, address and telephone details will not be included in these records. The data collected will be stored for a minimum of 10 years, or as stated by the study Sponsor, whichever is longer.

The information from the study may be published or sent to regulatory authorities in your country or other countries where regulatory approval for the medication is required. Your identity will not be released except with your permission, unless necessary for the vital interests of your safety.

We use personally-identifiable information to conduct research to improve health and care. As a pharmaceutical we have a legitimate interest in using information relating to your health and care for research studies, when you agree to take part in a research study. This means that we will use your data, collected in the course of a research study, in the ways needed to conduct and analyse the research study. Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you

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withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

If you wish to raise a complaint on how we have handled your personal data, you can contact our Data Protection Officer who will investigate the matter. If you are not satisfied with our response or believe we are processing your personal data in a way that is not lawful you can complain to the Information Commissioner's Office (ICO). You can contact the Data Protection Officer at dataprivacy@theravance.com.

By signing this consent form, you are giving permission for the processing and use of your personal information for this study during the study and after the end of the study. You are also giving permission for the processing of your personal information or any part of it to be transferred to people and organisations (mentioned above) or to be processed and used in IT systems outside the UK, where personal data protection laws may be less strict. You can also request a copy of data transfer clauses if your personal data is shared outside the EU. Please contact the study centre in case you want to exercise these rights. The study centre will align with the Sponsor to handle your request. When we send your personal information to another country, the way we do it is either controlled by a contract approved by data privacy authorities or by Theravance Biopharma Ireland Limited own privacy rules which have been approved by privacy authorities (called Binding Corporate Rules).

Your study doctor may tell your family doctor about you taking part in the study and ask them for medical information about you.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

There is no expiration date to this statement.

What will happen to the results and this clinical study?
The results of this study may be used to learn more about snOH, or to develop or improve treatments for this condition in the future. The results of this study may also be published or announced. However, you will not be identified in any publications or announcements.
The results of this study will be used to make informed clinical decisions for developing this new medication. If you want the results to be made available to you, please talk to your study doctor.

Who has reviewed the study?
All research studies are reviewed by an independent group of people, called a research ethics committee to protect your safety, rights, well-being, and dignity. This study has been reviewed and has been given a favourable opinion by the Wales Research Ethics Committee 1.

The sponsor, regulatory authorities or the ethics committee may stop the study at any time where there is good reason.

It has also been reviewed and approved by the UK regulatory body, the Medicines and Healthcare products Regulatory Agency (MHRA).

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Who can I contact for more information?

For more information please contact:

Study Doctor Name: **Re:Cognition Health**

Study Doctor Phone: **020 3355 3536**

Study Coordinator Name: **Re:Cognition Health**

Study Coordinator Phone: **020 3355 3536**

Emergency Out of Hours contact Name: **Dr Emer MacSweeney**

Emergency Out of Hours Contact Number: **075 4080 2222**

[England only] Patient Advice and Liaison Service (PALS) Number: **N/A**

Thank you for reading this and considering if you will take part in this study.

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<<to be placed on hospital headed paper>>

Consent form

Study title: A Phase 3, 4-week, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Study of TD-9855 in Treating Symptomatic Neurogenic Orthostatic Hypotension in Subjects With Primary Autonomic Failure

Study protocol: 0169

Study drug: TD-9855, referred throughout the document as the "study drug"

Sponsor of the study: Theravance Biopharma Ireland Limited, Connaught House, 1 Burlington Road, Dublin 4, D04 C5Y6, Ireland

Investigator: Dr Emer MacSweeney

Patient Name: _____

Patient Number: _____

I confirm the following:

• I have read (or someone has read to me) and understand the information sheet for the above study and have had enough time to think about taking part.	*Patient initial*
• I am satisfied with the answers given to all my questions.	*Patient initial*
• I voluntarily agree to be part of this research study, to follow the study procedures and to provide the information the study doctor, nurses or other staff members ask from me.	*Patient initial*
• I understand that I am free to withdraw from this study at any time without giving a reason and without my medical care or rights being affected.	*Patient initial*
• I agree that if I decide to withdraw and leave the study, the information and data collected about me up to the point when I withdraw may continue to be used.	*Patient initial*
• I have received a copy of this information sheet and consent form to keep for myself.	*Patient initial*
• I agree if my study doctor is not my family doctor, my family doctor may be told about my taking part in this study and asked for medical information about me and may provide details of my past medical history to the study. They might also be contacted by site staff in the event that contact with me is lost during the study.	*Patient initial*
• I agree to my samples being taken and used as described in this information sheet	*Patient initial*
• I give permission for my personal information , including my age, sex, race and ethnicity, to be collected and used as part of this clinical study and to be: - identified only with my study patient number; - reviewed, processed and disclosed by and to the sponsor, its authorised representatives and study monitors for the purposes described in the study protocol; - reviewed or audited by appropriately authorised organisations and other persons and entities identified on this form; - published and sent to regulatory authorities or health insurers in my country or other countries; and - transferred if required to any country, where laws protecting my personal information may be different to my own.	*Patient initial*
• I understand I may also be contacted at a later date(s) for my permission in connection with this or any related sub study (please initial yes or no).	*Patient initial* *YES* / *Patient initial* *NO*

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By signing this document, I agree to take part in this study, as set out in this information sheet and consent form.

I understand that my legal rights are not affected by signing this consent form.

There is no expiration date for this consent form.

Patients Name (or the name of my representative):

Signature (Patient or representative): Date: DD-MMM-YYYY

Investigator/Authorised Designee:

- ✓ I have fully and carefully explained the study to the person named above and confirm that, to the best of my knowledge, they clearly understand the nature, risks and benefits of taking part in this study.
- ✓ I confirm that I gave them all opportunities to ask questions about the study, and that I answered all the questions they asked correctly and to the best of my ability.
- ✓ I confirm that they have not been forced into giving consent, and that they have given their consent freely and voluntarily.
- ✓ I confirm they have been given a copy of this information sheet and consent form.

Name of Investigator/Designee:

Signature of Investigator/Designee: Date: DD-MMM-YYYY