A Physician-Initiated Multiple-Dose, Single Period, Phase 0-I Dose Ranging Study to Examine Levellor™ HypoSpray Human Insulin Adult Healthy Volunteer Patients

Protocol No.: LEV 101-D-022521
ClinicalTrials.gov Reference NCT04857320

21st APRIL, 2021

Version 1.3

SPONSOR: Langford Research Institute

Principal Investigator: William D. Kirsh, D.O., M.P.H.

Approved by Langford Research Institutional Review Board April 21st, 2021

AMENDMENTS:

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Contents

List of abbreviations

AE	adverse event
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the curve
BP	blood pressure bpm
	beats per minute
BUN	blood urea nitrogen
C_{max}	maximal plasma concentration
CPK	creatinine phosphokinase
CNS	central nervous system
CRF	case report form
EPI	Human Insulin(Adrenalin)
EU	European Union
GCP	Good Clinical Practice
GP	General Practitioner
HIV	human immunodeficiency virus
HPS	HypoSpray® proprietary transdermal delivery system (TDS)
ICH	International Conference on Harmonization of Technical
	Requirements for Registration of Pharmaceuticals for Human Use
IUCD	Intrauterine Contraceptive Device
LDH	lactate dehydrogenase
LFT	Liver Function Test
MHRA	Medicines and Healthcare products Regulatory Agency
mm Hg	millimeters of mercury
NCR	no carbon required
NRS	numerical rating scale
OECD	Organisation for Economic Co-operation and Development
PI	Principal Investigator

PK	Pharmacokinetics
RBC	red blood cells
REC	Research ethics committee
SAP	Statistical analysis plan
SAE	Serious adverse event
SGOT	serum glutamic oxaloacetic transaminase (same as AST)
SGPT	serum glutamic pyruvic transaminase (same as ALT)
SUSAR	serious unexpected suspected adverse reaction
$T_{1/2}$	plasma concentration half life
TDS®	Proprietary transdermal drug delivery system
T_{max}	time passed since administration at which the maximum plasma concentration occurs
WBC	white blood cells (leukocytes)
WHO	World Health Organization

1.0 Synopsis

Name of medicinal product/active substance	Levellor™ HypoSpray Human Insulin 100 IU/mL
Title of the Study	A Multi-Dose, Cross-over, Phase 0 Dose Ranging Study to Compare Levellor HypoSpray Human insulin in Healthy Volunteers.
Protocol Number/Clinical Phase	Protocol No.: LEV 001-D-020521 Phase 0-1
Chief Investigator	William Kirsh, D.O., M.P.H.
Study Site	Clinical Studies Unit
Rationale	A new formulation of Human Insulin (Levellor™ HypoSpray) utilizes the HDS HypoSpray® drug delivery system (HypoSpray Pharma, Florida, USA) which is a novel, proprietary transdermal technology, developed for use in pharmaceutical, cosmetic and over-the-counter products. Transdermal administration combines a rapid onset of action with a convenient and patient-friendly, and in this case needle-less method of administration, which, it is believed, will provide enhanced safety as a more rapid and long lasting physiological-response alternative to the traditional SC Injectable route for the administration of Insulin. This study will assess the volunteer response to increasing doses of Human Insulin Levellor HypoSpray at various doses p.r.n. compared against SC injection at various sites of application and under varied conditions.
Objectives	The primary objective is to determine the amount of lowering serum glucose and dose response to a topically applied formulation of Human Insulin (Levellor™ HypoSpray) administered by spraying onto adult Healthy Volunteer subjects as compared to no treatment. A 2-week period of daily blood sugar monitoring and insulin dosing for 3 days then monitoring for 3 days following will form the baseline data or each subject. The secondary objective is to evaluate the tolerability and local and systemic effects of Levellor™ HypoSpray.
Design:	This is a non-randomized, open label single period, phase 0l study.

Duration of treatment:	The maximum study duration is 20 days.

Study Population:	Adult Male patient volunteers aged 20 to 60 years.
Main Criteria for Inclusion	1. Healthy Adult Males 2. 20 and 60 years of age, inclusive. 3. The subject has a serum protein A1C of less than 6. 4. The subject is willing and able to read, understand the Subject Information Sheet and provide written informed consent. 5. The subject has a body mass index (BMI) within 18-50 kg/m^2. 6. The subject is in otherwise good health as determined by medical history and physical examination. 7. The subject is a non-smoker. 8. The subject must agree to continue with daily serum glucose testing by means of a wearable blood glucose for the pharmacokinetic assessments. 9. The subject is willing and able to comply with all testing and requirements defined in the protocol. 10. The subject is willing and able to return to the study site for all visits.

Main Criteria for Exclusion:	1. The subject has any relevant deviations from normal other than blood glucose in physical examination, electrocardiogram (ECG), or clinical laboratory tests, as evaluated by the investigator. 2. The subject has had a clinically significant illness within 30 days preceding entry into this study. 3. The subject has a history of significant neurological, hepatic, renal, endocrine, cardiovascular, gastrointestinal, pulmonary, or metabolic disease. 4. The subject has a known allergy or history of hypersensitivity to Human Insulin or similar modified Insulin compounds. 5. The subject has used any prescription medication that may interfere with the evaluation of study medication. 6. The subject has donated or lost a significant volume of blood (>450 mL) within four (4) weeks of the study, and their Haemoglobin concentration and hematocrit have not returned to within 5% of normal. 7. The subject has a history of substance abuse or a current positive urine drug screen or urine alcohol test. 8. Alcohol consumption greater than community norms (i.e. more than 21 standard drinks per week for males). 9. Subjects who have received an investigational drug or have used an investigational device in the 30 days prior to study entry
Concomitant Medication Restrictions	The intake of any medications (OTC or prescription) will be vigorously discouraged except as required to maintain health.
Total expected number of subjects	Sufficient volunteers will be recruited so as to obtain 5 completed subjects. Up to two additional subjects may be added.

Study Drug	The investigational medicinal product is Human Insulin (Levellor HypoSpray L). Three dose ranges will be assessed: administered via sprays from a syringe. Doses will be calculated from what the literature reports is the low end of Healthy Volunteer Insulin Sensitivity. The 3 doses will be 0.075 IU/KG body weight, 0.1 IU/KG Body weight and 0.15 IU/KG Body Weight. This will result in dose ranges of 5 to 20 IUs.

Randomization	Subjects will not be randomized. Sites of application: applied topically to the neck/chest arm, thigh area or inner aspect of a forearm.
Dosage	Patients will receive dosing from the investigator and document blood sugar with a wearable Continuous Glucose Monitor (Libre 2) and will be dosed for 3 days. The monitor will be worn for 24 hours before the first dose and longer if available up to 7 days before beginning the study routine and 3 days after and receive the study drug via topical application for three days.
Criteria for evaluation:	**Pharmacokinetics** ***Primary pharmacokinetic variables*** The primary pharmacokinetic variables include: the reduction of serum glucose from baseline and at typical post prandial spikes and the amount of insulin necessary to accomplish this reduction. In addition to 90% confidence intervals, the data will be summarized by medians, and maximum and minimum values. The elimination half-life of Insulin will be compared using non-transformed data and parametric techniques. Averages for the serum glucose and Post prandial excursions will be compared against averages for experimental periods.
Safety and Tolerability	Adverse Events will be recorded throughout the study, at all visits and during any telephone calls. Details on medical history and concomitant illnesses will be recorded on the day of screening by conducting a medical interview of subject or subject relative(s) and/or review of the subject's medical records. Any changes observed or reported during the study will be recorded. A brief physical examination will be performed at Screening and at the Final Visit. Clinical laboratory tests will be performed at Screening, and on the days of Human Insulin administration, serum glucose levels will be monitored by means of a wearable Continuous Glucose Monitor.

2.0 Flow Chart

Study Day Activity	Visit 1 Screening	Visit 2 First Dose	Visit 3 Second Dose	Visit 4 Last Dose	Visit 5 Discharge
Informed consent	X				
Inclusion/exclusion criteria	X	X	X	X	X
Demography	X				
Medical history	X				
Brief physical examination	X				
Vital signs	X	X		X	X
Concomitant medication	X	X		X	
Local skin evaluation: clinical	X	X		X	
Hematology, biochemistry and urinalysis	X	X		X	
Serum Glucose Profile Test*	X	X	X	X	X
Urine Drug Screen	X				
Randomization	X				
Topical Dose		X	X	X	
Patient Questionnaires					X
Adverse events		X	X	X	X

* Normal pre and post meal and pre- and post bedtime Time Points as measured by the CGM

Confidential

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VOLUNTEER DOCLOSURES

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Appendix 2 **Subject Information Sheet and Informed Consent**

(Form to be on headed paper)

Study Number: LEV 101-D-022521
Subject Identification Number:

Study title:

A Physician-Initiated , Multiple-Dose, Single Period, Phase 0-I Dose Ranging Study to Examine Levellor™ HypoSpray Human Insulin Adult Healthy Volunteer Patients

IND No: N A P h a s e 0
Sponsor: Langford Research Institute
Version number: 1.0

Part 1

Invitation

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish.

- Part 1 tells you the purpose of this study and what will happen to you if you take part.
- Part 2 gives you more detailed information about the conduct of the study.

Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

The Langford Institute is the sponsor of this research.

What is the purpose of the study?

The purpose of the study is to measure the extent of the absorption (through the skin and into the blood) of several doses of Human Insulin from a new formulation of this well-known medicine. It is believed that the new transdermal route i.e. through the skin, will provide a rapid onset of action, and be more convenient and user-friendly than the traditional injection route for the administration of Human Insulin. This study will examine your blood glucose response profiles to Human Insulin applied via the skin with a new delivery

technology as compared to injection.

Why have I been approached?

You are being asked to take part in this study because you are an adult aged between 20 and 60 years and in good health, particularly without Type 1 or 2 Diabetes Mellitus.

Do I have to take part?

No. It is up to you to decide whether or not to take part. If you do, you will be given this information sheet to keep and be asked to sign a consent form. You are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?

If you agree to take part, you will be required to attend the clinic on four (4) occasions to see the doctor/nurse. Two (2) of these visits will last only an hour each. The total study period for most will be a maximum of 35 days including the screening visit. A minimum of 7 volunteers will be recruited to the study.

The requirements of the study and your participation are described as follows:

At every visit we will check your general health and perform a brief physical examination, including blood pressure and pulse rate.

Screening Visit

(This will occur no more than 28 days before the first administration of study medication)

If you agree to take part and to sign a “Consent for Study Screening” you will be invited to a selection session with the Endocrine Investigations Unit.

You will be examined by the study doctor, who will take a detailed medical history and conduct a brief physical examination, including blood pressure and pulse rate and we will ask you about your medication and ask about any drug and/or alcohol abuse. We will ask you to provide a urine sample to test for drugs of abuse.

Before joining the study we will require a 30mL blood sample from your arm for routine safety tests (about six (6) tablespoons.

With your permission we will contact your General Practitioner to advise them of your potential participation in this study.

Visit 2 – Baseline

Once accepted into the study, we will ask you to come to the Clinical Trials Unit in the early morning. At this time you will undergo a check-in procedure and sign a "Consent for Study Participation".

We will start by applying the wearable continuous glucose monitor CGM (a small button with a small size needle) into your arm if you haven't already done so, by following the instructions on the package. By using the CGM we will be able to take monitor small samples of blood without having to keep using a needle each time. After the last sample day, the CGM button can be removed.

The Human Insulin dose will be sprayed topically by you on to the upper chest, or your forearm or thigh and you will be asked to rub it in gently. At 60 minutes after application we will poll the CGM for a reading. The blood sampling by the CGM is to calculate your response to Human Insulin as measured by a shift in serum glucose. We will also measure your heart rate and blood pressure at regular intervals.

A digital photograph will be taken of the application site prior to administration and after 30 minutes. The purpose of the photograph is to both carefully assess the application site and to keep a record of this; you will not be identifiable from the photograph.

We will also measure your heart rate and blood pressure.

During the day you can stay within the Unit but are not required to. It is most important that you are relaxed and are not stressed or excited as this may alter your own natural Human Insulin production and confuse the study results. You should plan to eat lunch at the same time each of the 3 dosing days and you should try to eat roughly the same thing each day.

In between dosing visits

We will call you by telephone at an agreed time between Visits 2 and 3 to confirm your continued participation, daily dose schedule and eligibility (including concomitant medication use) as well as the occurrence of adverse events.

Visit 5 (Final dose) - Day 6+

We will ask you to come to the Clinical Trials Unit in the early morning. At this time you will undergo a check-in procedure.

We will start by polling the CGM in your arm. The blood samples on this day are to calculate whether you are returning to your normal pattern of glucose rising before to just after and falling after meals has resumed. We will also measure your heart rate and blood pressure at regular intervals. After the last polling, the CGM can be removed.

During the day you can stay within the Unit or leave to work or read quietly. It is most important that you are relaxed and are not stressed or excited as this may alter your own natural Human Insulin production and confuse the study results.

A digital photograph will be taken of the application site prior to the final administration of the Human Insulin spray and again after 60 minutes.

After the last blood collection, the CGM can be removed, you will be assessed and then may go home.

What do I have to do?

If you choose to take part in this study you must not be taking part in other study. You must also not have taken part in any other study within the last 30 days.

You will need to come to the Clinical Trials Center at the times requested and remain there for the duration of time required for each visit.

You must inform your research doctor of all other medications you are taking including over the counter medications. You should not take any medications without first consulting the research doctor or nurse.

If you experience any changes in your health whether or not you feel that this is related to your study medication, then you must inform your research doctor.

What is the drug, device or procedure that is being tested?

The HypoSpray Pharma System (HypoSpray®) is a combination of harmless chemicals at very low doses, which are balanced to deliver drugs through the skin without a needle, pain or irritation. These chemicals are usually used in cosmetics foods and food supplements. The HDS® system releases the drug where it is intended to have its effect without changing the drug in any way.

Human Insulin is the hormone that the body creates to stimulate the conversion of fat to sugars the body needs for energy. The hormone is critical in helping the body manage dietary glucose metabolism.

What are the alternatives for diagnosis or treatment?

There are no alternative treatments to Human Insulin except the injectable form. In the unlikely event of a reaction, you will be treated with the appropriate remedy which might be a dose of glucose or other sugar by means of eating or drinking a sugary foodstuff or drink like a soft drink. The medicines being used in the study are believed to be the easiest and least invasive to use.

What are the side effects of any treatment received when taking part?
Most Common: Application site reaction, abnormal lab test results. The severity of these side effects usually depends on the size of the dose of Human Insulin and may continue throughout the study.

Less common: Headache, dizziness, hypoglycemia and problems passing water.

Very Rare: Heart attack or stroke. We do not expect this, but it is possible.

What are the other possible disadvantages and risks of taking part?
The chemicals used in all of the HypoSpray® system are mainly used in the cosmetics and foods industries and are known to be safe for skin application. Additionally, we will be using them at very low concentrations compared to other products. We have recently finished two studies using HypoSpray ® with local anesthetics in 100 volunteers HypoSpray ® with Testosterone in a further 17 volunteers and HypoSpray ® with Diazepam in 12 volunteers, a skin safety study in 32 volunteers with no side effects.

There are very few risks involved in inserting a continuous glucose monitor probe into a vein in the arm. You may feel some discomfort and sometimes there may be a small bruise around the area, which may be sore and last for a couple of days.

Harm to the unborn child
The effects of Human Insulin on the unborn child may be harmful. *You should be careful to avoid making skin-to-skin contact while the skin is* still wet after dosing, with anyone who is or might be pregnant while you are participating in this trial.

What are the possible benefits of taking part?
This study may not benefit you directly; however it may lead to the development of a more effective transdermal (delivery through the skin) version of Human Insulin.

What happens when the research study stops?
You will be free to go home.

What if there is a problem?
Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in part 2.

If you have a complaint, please contact the following person: Dr. William Kirsh.

If you feel any discomfort or distress during the investigations, you must say so and we will stop the tests immediately at any time.

If you are employed by Langford Research, non-participation or dropping out of the

study will not affect your training or career.

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2.

A contact number for complaints will be given.

Will my taking part in the study be kept confidential?
Yes. All the information about your participation in this study will be kept confidential. The details are included in Part 2.

Contact Details:
If you require any further information, please contact:

Name of Doctor: Dr. William Kirsh
Tel Number: 786-382-3310

Or:

After-hours number: 786-382-3310

This completes Part 1 of the Information Sheet.

If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.

Part 2

What if relevant new information becomes available?
Sometimes, during the course of a research project, new information becomes available about the treatment/drug that is being studied. If this happens, your research doctor will tell you about it and discuss whether you want to or should continue in the study. If you decide not to carry on, your research doctor will make arrangements for your care to continue. If you decide to continue in the study, you will be asked to sign an updated consent form.

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

If the study is stopped for any other reason, you will be told why, and your continuing care will be arranged.

What will happen if I don't want to carry on with the study?
If you withdraw from the study, we will need to use the data collected up to your withdrawal. We would ask you to keep in contact with us to let us know your progress. Information collected may still be used. Any stored blood or tissue samples that can still be identified, as yours will be destroyed if you wish.

If your participation in the study is discontinued after you have started taking the study drug you will be asked to undergo a final examination for your own safety. If the reason for ending the study is, for example, an adverse event or a side-effect of the drug, you will be asked to give information on these in order to protect the other patients taking part in this clinical study.

What if there is a problem?
If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action, but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you.

Complaints:
If you have a concern about any aspect of this study, you should ask to speak with the Research Doctor who will do their best to answer your questions (Dr. William Kirsh, telephone: 786-382-3310). If you remain unhappy and wish to complain formally you can do this by contacting:
The Complaints Officer: c/o Chief Operating Officer for the Clinical Unit Center.

Will my taking part in this study be kept confidential?
All the information obtained about you in the course of the study is confidential according to rules and will be kept in a secure locked room. The investigators performing the study and a study Monitor will have access to the data collected in this study. They may also be looked at by representatives of regulatory authorities and by authorised people from the Institute to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and nothing that could reveal your identity will be disclosed outside the research site.

Involvement of the General Practitioner/Family doctor (GP)
With your permission we will contact your General Practitioner to advise them of your potential participation in this study.

What will happen to any samples I give?
All your blood and urine samples taken for safety screening and for drugs of abuse will be tested immediately in the clinical lab and once the results are obtained, they will be destroyed.

Will any genetic tests be done?

No genetic tests will be done for this study.

What will happen to the results of the research study?
The results of this study may be published or presented at meetings. You will not be identified in any report / publication or presentation.

Who is organizing and funding the research?
This research is being sponsored by HypoSpray Pharma.

Who has reviewed the study?
This study has been given a favorable ethical opinion for conduct in the Research Ethics Committee of the Langford Research Institute.

Before you sign this consent form, please ask any questions you have about the study. Thank you for taking the time to read this information sheet.

Study Number: LEV 101-D-022521 Phase 0
Subject Identification Number: _____

SCREENING CONSENT FORM

Title of Project:

A Multiple-Dose, Single Period, Phase 0-I Dose Ranging Study to Examine HDS®-Human Insulin in Adult Subjects

Name of Researcher: Dr. William Kirsh

Please initial box

1. I confirm that I have read and understand the information sheet dated ..... , (version .....) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐
3. I understand that relevant sections of any of my medical notes and data collected during the study, may be looked at by responsible individuals from Clinical Studies Center and from regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records and understand that my records will be maintained confidential.	☐
4. I agree to my GP being informed of my participation in the study if necessary.	☐
5. I agree to take part in the above study.	☐

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of Person Taking Consent	Date	Signature
_____	_____	_____
Name of Researcher	Date	Signature

Study Number: LEV 101-D-022521 Phase 0
Subject Identification Number: _____

STUDY CONSENT FORM

A Multiple-Dose, Single Period, Phase 0-I Dose Ranging Study to Examine Human Insulin HypoSpray in Adult Subjects

Name of Researcher: Dr. William Kirsh

Please initial box

1. I confirm that I have read and understand the information sheet dated ..... , (version .....) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
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Name of Patient	Date	Signature
_____	_____	_____
Name of Person Taking Consent	Date	Signature
_____	_____	_____
Name of Researcher	Date	Signature