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An open-label mass balance study of [14C]NST-6179 in healthy male subjects

Submission date 25/05/2024	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 12/07/2024	**Overall study status** Completed	
Last Edited 26/11/2024	**Condition category** Digestive System	

Plain English summary of protocol

Background and study aims
The Sponsor is developing the test medicine, NST-6179, as a potential treatment for intestinal failure associated liver disease (IFALD), also referred to as parenteral nutrition associated liver disease. IFALD is a liver injury that occurs in patients with intestinal failure who are dependent on a lifesaving treatment called Parenteral Nutrition. Parenteral nutrition (PN) is a lifesaving treatment for individuals with intestinal failure (where food is not digested or absorbed properly). This is a way of providing food and nutrients needed in the body by adding them directly into the bloodstream through a vein. However, long-term PN treatment can have potentially serious problems, including liver disease.

In this study, we'll give healthy volunteers a single dose of test medicine to find out how the body breaks down and gets rid of the test medicine. The test medicine will be 'radiolabelled' - it will contain a small amount of radioactivity (Carbon-14) - so that we can track it in the body.

In this study in healthy volunteers, we aim to answer these questions.
* Does the test medicine cause any important side effects?
* How much test medicine enters the bloodstream and how quickly does the body get rid of it?
* How does the body break down and get rid of the test medicine?

Who can participate?
We plan to enrol up to 8 healthy men aged 30-65 years.

What does the study involve?
Volunteers will receive a single dose of radiolabelled test medicine, [14C]NST-6179, as 2 capsules by mouth. They'll stay in the clinic for up to 10 nights, and take up to 5 weeks to finish the study.

We'll collect blood and urine samples to do safety tests. Over a period of at least 8 days, and up to a maximum of 10 days, we'll take many blood samples and volunteers will collect all their urine and faeces so that we can measure the amount of test medicine and its breakdown products.

What are the possible benefits and risks of participating?
Benefits:
Participants will get no medical benefit from taking part in this study. We hope that the development of a potential treatment for intestinal failure associated liver disease (IFALD), also referred to as parenteral nutrition associated liver disease, will be of benefit to patients with this condition.
Risks:
Volunteers may experience side effects from the test medicine. Full information on possible side effects is in the Participant Information Sheet and Informed Consent Form. There is always a risk of unexpected side effects or an allergic reaction. To mitigate the risk, we'll ensure that volunteers meet the entry criteria for the study and monitor volunteers closely throughout the study.

Volunteers will receive a maximum effective dose of radiation of 0.8 milliSieverts (mSv) due to the radioactivity administered in the capsules, which is equivalent to about 3.6 months exposure to average background radiation in the UK (2.7 mSv). That amount of radiation poses negligible risk to the volunteers' health but volunteers should not take part in any other study involving radiation for at least 1 year.

Our screening tests might be of benefit if we find an important medical problem, but they might reveal something that the volunteer would prefer not to know about. If there are medically important findings in our tests at screening, or during the study, we will inform the volunteer's GP.

Volunteers will be confined to the clinic during the study and must make outpatient visits and comply with the lifestyle restrictions described in the PIS-ICF, including periods of fasting from food and drink except water, and short periods during which they'll be allowed no fluids.
The test medicine might harm unborn children, so all volunteers must follow the restrictions on donation of sperm and use acceptable contraception. Were a partner of a volunteer to become pregnant during the study, we would ask permission to follow up the pregnancy.
Volunteers will undergo many tests and procedures during the study.
*Blood sampling can cause soreness and bruising of the arms but these problems usually clear up within a few days to a few weeks. Susceptible volunteers may faint when we take blood samples; volunteers must lie down when we take blood samples to mitigate that risk.
*ECG stickers may cause local skin irritation.
Healthy volunteers will get no medical benefit from the test medicine; however, the aims of the study can be most efficiently met in volunteers with no concurrent medical conditions and who do need to take concomitant medication that might interfere with the study objectives or increase the risk of the study. The risk/benefit evaluation in this study supports the use of healthy volunteers.
Volunteers will receive payment for participating in the study. There is always a risk that payment could represent coercion. However, payment will be based on committed time, inconvenience, and travel and other expenses, not on risk. An ethics committee will review the payment to ensure that it is fair.

Where is the study run from?
Quotient Sciences Limited (UK)

When is the study starting and how long is it expected to run for?
May 2024 to August 2024

Who is funding the study?
NorthSea Therapeutics B.V. (Netherlands)

Who is the main contact?
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Contact information

Type(s)
Public, Scientific

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Additional identifiers

Integrated Research Application System (IRAS)
1009695

Protocol serial number
NST-6179-03

Study information

Scientific Title

A phase I, open-label, single-period, single-dose study to assess the absorption, metabolism, and excretion of oral [14C]NST-6179 (Orziloben) in healthy male subjects

Study objectives
Primary objectives:
1. To determine routes and rates of elimination and mass balance of total radioactivity (TR) after a single oral dose of [14C]NST-6179
2. To characterise the PK (pharmacokinetics) of NST-6179 in plasma and TR in plasma and whole blood following a single oral dose of [14C]NST-6179

Secondary objectives:
1. To perform metabolite identification and profiling in plasma, urine and faeces
2. To evaluate the extent of distribution of TR into blood cells
3. To provide additional safety and tolerability information for NST-6179

Ethics approval required
Ethics approval required

Ethics approval(s)
Submitted 23/05/2024, HSC REC B (Business Services Organisation, Unit 5, Lissue Industrial Estate West, Rathdown Walk, Moira Road, Lisburn, BT28 2RF, United Kingdom; +44 28 9536 1400; RECB@hscni.net), ref: 24/NI/0061

Primary study design
Interventional

Study design
Interventional single centre study to assess absorption metabolism and excretion

Study type(s)
Other

Health condition(s) or problem(s) studied
Intestinal failure associated liver disease (IFALD), also referred to as parenteral nutrition (PN) associated liver disease, and other potential indications.

Interventions
This is a non-randomised, open-label, uncontrolled study. Volunteers will receive a single dose of radiolabelled test medicine, [14C]NST 6179, as 2 capsules by mouth. They'll stay in the clinic for up to 10 nights and take up to 5 weeks to finish the study.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
[14C]NST-6179 capsule, 300 mg (NMT 3.35 MBq) [Orziloben]

Primary outcome(s)
1. Mass balance recovery of total radioactivity in urine, faeces and all excreta of the test medicine from the body from samples taken from Day 1 up to a maximum of Day 10
2. Pharmacokinetics and total radioactivity of the test medicine in plasma and whole blood measured in blood samples taken from Day 1 up to a maximum of Day 10

Key secondary outcome(s)
1. Identify the metabolic profile (breakdown products) of the test medicine in plasma, urine and faeces in samples taken from Day 1 up to a maximum of Day 10.
2. Evaluation of whole blood:plasma concentration ratios for total radioactivity (to evaluate the extent of distribution of total radioactivity into blood cells), using samples taken between Day 1 up to a maximum of Day 10.
3. Adverse events (to assess tolerability of the test medicine) will be collected by asking volunteers how they are feeling, from the start of the trial until follow-up. Other safety measures (including vital signs, ECGs and laboratory safety tests) will also be assessed by standard phase I unit monitoring, at screening, from Day 1 to discharge from the ward.

Completion date
23/08/2024

Eligibility

Key inclusion criteria
1. Must provide written informed consent.
2. Must be willing and able to communicate and participate in the whole study.
3. Aged 30 to 65 years inclusive at the time of signing informed consent.
4. Must agree to adhere to the contraception requirements defined in the protocol.
5. Healthy males according to the assessment of the investigator, as based on a complete medical history including a physical examination, vital signs, 12-lead ECG, and clinical laboratory tests without any clinically significant abnormalities.
6. Body mass index (BMI) of 18.0 to 32.0 kg/m^2, inclusive, as measured at screening.
7. Must have regular bowel movements (i.e. average stool production of ≥1 and ≤3 stools per day).

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
30 Years

Upper age limit
65 Years

Sex

Male

Key exclusion criteria

1. Serious adverse reaction or serious hypersensitivity to any drug or formulation excipients.
2. Presence or history of clinically significant allergy requiring treatment, as judged by the investigator. Hay fever is allowed unless it is active.
3. History of clinically significant cardiovascular, renal, hepatic, dermatological, chronic respiratory or GI disease, neurological or psychiatric disorder, as judged by the investigator.
4. Subjects who do not have suitable veins for multiple venepunctures/cannulation as assessed by the investigator or delegate at screening.
5. Clinically significant abnormal clinical chemistry, haematology or urinalysis as judged by the investigator (laboratory parameters are listed in the protocol). Subjects with Gilbert's Syndrome are not allowed.
6. Positive hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (HCV Ab) or human immunodeficiency virus (HIV) 1 and 2 antibody results.
7. Evidence of renal impairment at screening, as indicated by an estimated creatinine clearance (CLcr) of <80 mL/min using the Cockcroft-Gault equation.
8. Subjects who have received any IMP in a clinical research study within the 90 days prior to Day 1, or less than 5 elimination half-lives prior to Day 1, whichever is longer.
9. Radiation exposure, including that from the present study, excluding background radiation but including diagnostic x-rays and other medical exposures, exceeding 5 mSv in the last 12 months or 10 mSv in the last 5 years. No occupationally exposed worker, as defined in the Ionising Radiation Regulations 2017, shall participate in the study.
10. Subjects who have been administered IMP in an ADME study in the last 12 months.
11. Donation of blood or plasma within the previous 3 months or loss of greater than 400 mL of blood.
12. Subjects who are taking, or have taken, any prescribed or over-the-counter drug or herbal remedies, including topical medications, (other than up to 4 g of paracetamol per day in the 14 days prior to Day 1, or less than 5 elimination half-lives prior to Day 1, whichever is longer). Exceptions may apply, as determined by the investigator, if each of the following criteria are met: medication with a short half-life if the washout is such that no pharmacodynamic activity is expected by the time of dosing with IMP; and if the use of medication does not jeopardise the safety of the trial subject; and if the use of medication is not considered to interfere with the objectives of the study. COVID-19 vaccines are accepted concomitant medications.
13. Subjects who are using medications or products that are inhibitors or inducers of CYP2C9 or uridine 5'-diphospho-glucuronosyltransferase (UGT) in the 14 days (for CYP2C9/UGT inhibitors) /28 days (for CYP2C9/UGT inducers) prior to Day 1, or less than 5 elimination half-lives prior to Day 1, whichever is longer.
14. Use or intention to use any medications or products known to alter drug absorption, metabolism, or elimination processes, including St John's Wort, in the 30 days prior to Day 1. Exceptions may apply, as determined by the investigator.
15. History of any drug or alcohol abuse in the past 2 years.
16. Regular alcohol consumption in males >21 units per week (1 unit = ½ pint beer, or a 25 mL shot of 40% spirit, 1.5 to 2 units = 125 mL glass of wine, depending on type).
17. A confirmed positive alcohol breath test at screening or admission.
18. Current smokers and those who have smoked within the last 12 months.
19. Current users of e-cigarettes and nicotine replacement products and those who have used these products within the last 12 months.
20. A confirmed breath carbon monoxide reading of greater than 10 ppm at screening or admission.
21. Confirmed positive drugs of abuse test result (drugs of abuse tests are listed in the protocol)

at screening or admission.
22. Subjects with pregnant or lactating partners.
23. Subjects who are, or are immediate family members of, a study site or sponsor employee.
24. Failure to satisfy the investigator of fitness to participate for any other reason.

Date of first enrolment
22/07/2024

Date of final enrolment
24/08/2024

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Quotient Sciences Limited
Mere Way, Ruddington Fields
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United Kingdom
NG11 6JS

Sponsor information

Organisation
NorthSea Therapeutics B.V.

Funder(s)

Funder type
Industry

Funder Name
NorthSea Therapeutics B.V.

Results and Publications

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study are not expected to be made available due to commercial sensitivity

IPD sharing plan summary

Not expected to be made available