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A study in healthy volunteers to compare a new test medicine to an already marketed medicine when injected into the veins

Submission date
12/12/2024

Recruitment status
No longer recruiting

Registration date
02/01/2025

Overall study status
Completed

Last Edited
02/01/2025

Condition category
Injury, Occupational Diseases, Poisoning

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
The Sponsor is developing the test medicine NPJ5008 to treat a rare and life-threatening condition called fulminant hypermetabolic crisis (FHC) triggered by anaesthetic gases, antipsychotic medications or extreme exertion/exercise. Symptoms include muscle rigidity and increasing body temperature. There are currently no medicines marketed specifically to treat FHC.
The test medicine (NPJ5008) is given directly into the veins and contains the active ingredient dantrolene. Dantrolene is currently marketed in the EU as DANTRIUM IV®. This study will compare the new medicine to DANTRIUM IV®, the reference medicine used to treat malignant hyperthermia (FHC caused by exposure to anaesthetic gases).

Who can participate?
Healthy males and women (of non-childbearing potential only) volunteers aged 18 to 55 years

What does the study involve?
This is the first time the test medicine has been given to people. This study consists of two parts. Part 1 will compare the amount of dantrolene in the blood when NPJ5008 and DANTRIUM IV® are given to see if they are similar and see how safe and well-tolerated the test medicine is when given at a low dose. Part 2 will look at the safety and tolerability of higher doses of the test medicine, similar to the doses that would be given to patients. Part 1 will include up to 16 healthy volunteers attending two visits (screening, study period of 9 overnight stays). Each volunteer will receive a single 60 mg dose of the test medicine and a single 60 mg dose of DANTRIUM IV® in turn, with at least 5 days in between. Part 2 will include up to 10 healthy volunteers attending two visits (screening, study period of 4 overnight stays). Each volunteer will receive a single dose of either 120 mg or 240 mg of test medicine. Sentinel dosing will be used in both parts. A follow-up phone call will take place 5 to 7 days after the final dose to ensure the ongoing well-being of volunteers.

What are the potential benefits and risks of participating?
Volunteers will get no medical benefit from the test medicine NPJ5008 or the reference

DANTRIUM IV, however development of a treatment for FHC may benefit the population as a whole. The risk/benefit evaluation in this study supports the use of healthy volunteers. Full information on possible side effects is provided to volunteers in the Participant Information Sheet/Informed Consent Form. Volunteers are closely monitored during the study and safety assessments are performed regularly.

Where is the study run from?
Norgine, Ltd (UK)

When is the study starting and how long is it expected to run for?
January 2021 to July 2021

Who is funding the study?
Norgine, Ltd (UK)

Who is the main contact?
recruitment@weneedyou.co.uk

Contact information

Type(s)
Principal investigator

Contact name
Dr Litza McKenzie

ORCID ID
https://orcid.org/0000-0002-8828-8867

Contact details
Quotient Sciences
Mere Way
Ruddington
Nottingham
United Kingdom
NG11 6JS
+44 (0)330 3031000
recruitment@weneedyou.co.uk

Type(s)
Public

Contact name
Dr Richard Ng

Contact details
Norgine, Ltd
Norgine House
Widewater Place
Moorhall Road
Uxbridge

United Kingdom
UB9 6NS
+44 (0)1895453584
rng@norgine.com

Type(s)
Scientific

Contact name
Mr Jeff Pilot

Contact details
Norgine, Ltd.
Norgine House
Widewater Place
Moorhall Road
Uxbridge
United Kingdom
UB9 6NS
+44 (0)189 545 3736
JPilot@norgine.com

Additional identifiers

Clinical Trials Information System (CTIS)
2020-005719-35

Integrated Research Application System (IRAS)
292173

Protocol serial number
NPJ5008-01/2020 / QSC204721

Study information

Scientific Title
Single centre, two-part, part-randomised, open-label, intravenous, single-dose study designed to compare the relative bioavailability of novel intravenous NPJ5008 with DANTRIUM IV® in healthy volunteers

Study objectives
The trial will investigate the following primary, secondary and exploratory objectives:

Primary:
Part 1:
To demonstrate the bioequivalence of a novel NPJ5008 (test) vs DANTRIUM IV® (reference) in terms of overall exposure

Part 2:
To provide safety and tolerability information for NPJ5008 at higher doses than assessed in Part 1.

Secondary:
Part 1:
To determine the intravenous (IV) pharmacokinetics (PK - what the body does to the drug) of NPJ5008
To provide additional safety and tolerability information for NPJ5008

Part 2:
To determine the IV PK of NPJ5008

Exploratory Part 1 and Part 2:
To assess the dose linearity of the novel NPJ5008 IV formulation doses used in Parts 1 and 2

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 02/02/2021, Health & Social Care Research Ethics Committee A (HSC REC A) (Lissue Industrial Estate West, 5 Rathdown Walk, Moira Road, Lisburn, BT28 2RF, United Kingdom; +44 (0)28 9536 1400; RECA@hscni.net), ref: 21/NI/0013

Primary study design
Interventional

Study design
Two-part open-label single-center single-dose study: Part 1 of the study is randomized and Part 2 of the study is non-randomized

Study type(s)
Other, Safety

Health condition(s) or problem(s) studied
The Sponsor is developing the test medicine NPJ5008 to treat a rare and life-threatening condition called fulminant hypermetabolic crisis (FHC) triggered by anaesthetic gases, antipsychotic medications or extreme exertion/exercise. When triggered by anaesthetic gases the condition is better known as malignant hyperthermia (MH).

Interventions
This is a single-centre, two-part, part-randomised, open-label, IV, single-dose study in healthy male and female (women of non-childbearing potential only) subjects. Subjects who took part in Part 1 are not permitted to take part in Part 2. This is the first time the test medicine has been given to people. Part 1 will compare the amount of dantrolene in the blood when NPJ5008 and DANTRIUM IV® are given to see if they are similar and see how safe and well-tolerated the test medicine is when given at a low dose. Part 2 will look at the safety and tolerability of higher doses of the test medicine, similar to the doses that would be given to patients.

Part 1 will include up to 16 healthy volunteers attending two visits (screening, study period of 9 overnight stays). Each volunteer will receive a single 60 mg dose of the test medicine and a

single 60 mg dose of DANTRIUM IV® in turn, with at least 5 days in between. Part 2 will include up to 10 healthy volunteers attending two visits (screening, study period of 4 overnight stays). Each volunteer will receive a single dose of either 120 mg or 240 mg of test medicine. Sentinel dosing will be used in both parts when the test medicine is dosed.

Blood samples will be taken at selected time points throughout Part 1 and 2 for PK and safety laboratory assessments; urine samples for urinalysis will also be collected. Adverse event (AE) monitoring, vital signs including continuous peripheral oxygen saturation monitoring, 12-lead electrocardiograms (ECGs), hand grip tests, physical examinations and spirometry (as applicable per Part) will be performed at specified timepoints.

A follow-up phone call will take place 5 to 7 days after the final dose to ensure the ongoing well-being of volunteers.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
NPJ5008, DANTRIUM IV®

Primary outcome(s)
Part 1:
Statistical analysis of dantrolene AUC(0-last) and AUC(0-inf) values assessed from blood samples taken from pre-dose to up to 72 hours after dosing. This analysis includes adjusted geometric means for test and reference formulation, ratio of adjusted geometric means and corresponding 90% confidence intervals (CIs). If each of the 90% CIs lies within the acceptance interval of 80.00% to 125.00% then the formulations will be considered bioequivalent.

Part 2:
Safety and tolerability tests for both products by assessing: adverse events, vital signs including ECGs, hand grip tests, physical examinations and laboratory safety tests. Blood samples will be taken at selected time points from pre-dose until 72 hours post-dose for PK and safety laboratory assessments. Measurement of vital signs, electrocardiograms, laboratory safety tests and physical examinations will be done at screening and at intervals from admission until discharge.

Key secondary outcome(s)
Part 1 and Part 2:
Assessment of PK parameters (Tlag, Tmax, Cmax, AUC(0-6), AUC(0-72), AUC(0-last), AUC(0-inf), lambda-z, T1/2, CL, Vz, Cmax/D, AUC(0-last)/D and AUC(0-inf)/D) where analysis of the concentration-time data will be performed using appropriate non-compartmental techniques from plasma samples taken from pre-dose to 72 hours post final dose.

Part 1:
Safety and tolerability tests for the test product by assessing: adverse events, vital signs including ECGs, hand grip tests, physical examinations, spirometry and laboratory safety tests. Blood samples will be taken at selected time points from pre-dose until 72 hours post-dose for PK and safety laboratory assessments. Blood samples will be taken at selected time points

throughout Periods 1 and 2 for PK and safety laboratory assessments; urine samples for urinalysis will also be collected. Measurement of vital signs including continuous peripheral oxygen saturation monitoring, spirometry, 12-lead ECGs, hand grip tests and physical examinations will be done at screening and at intervals from admission until discharge.

Completion date
13/07/2021

Eligibility

Key inclusion criteria
1. Healthy males or females of non-childbearing potential
2. Aged 18 to 55 years, inclusive, at the time of signing informed consent
3. Body mass index (BMI) of 19.0 to 30.0 kg/m2 as measured at screening; subjects enrolled into the higher dose group in Part 2 (240 mg NPJ5008) may have a BMI of 19.0 to 32.0 kg/m2 as measured at screening
4. Weigh at least 55 kg
5. Must be willing and able to communicate and participate in the whole study
6. Must provide written informed consent
7. Must agree to adhere to the contraception requirements

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Upper age limit
55 Years

Sex
All

Total final enrolment
21

Key exclusion criteria
1. Subjects who have received any IMP in a clinical research study within the 90 days prior to first dose
2. Subjects who are, or are immediate family members of, a study site or sponsor employee
3. Subjects who have previously been administered IMP in this study
4. Subjects who have taken part in Part 1 are not permitted to take part in Part 2
5. Evidence of current SARS-CoV-2 infection
6. Upper respiratory tract infection in the 14 days before first IMP administration, pneumonia in

the 6 months prior to IMP administration
7. History of any drug or alcohol abuse in the past 2 years
8. Regular alcohol consumption in males >21 units per week and females >14 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)
9. A confirmed positive alcohol breath test at screening or admission
10. Current smokers and those who have smoked within the last 12 months. A confirmed breath carbon monoxide reading of greater than 10 ppm at screening or admission.
11. Current users of e-cigarettes and nicotine replacement products and those who have used these products within the last 12 months
12. Females of childbearing potential including those who are pregnant or lactating (all female subjects must have a negative highly sensitive urine pregnancy test at screening). A woman is considered of childbearing potential unless she is permanently sterile (hysterectomy, bilateral salpingectomy, and bilateral oophorectomy) or is postmenopausal (had no menses for 12 months without an alternative medical cause and a serum follicle stimulating hormone [FSH] concentration ≥40 IU/L)
13. Subjects who do not have suitable veins for multiple venepunctures/cannulation and IV infusions as assessed by the investigator or delegate at screening
14. Clinically significant abnormal clinical chemistry, haematology or urinalysis as judged by the investigator. Subjects with Gilbert's Syndrome are not allowed.
15.Subjects with AST, ALT or total bilirubin greater than the upper limit of norma
16. Confirmed positive drugs of abuse test result
17. Positive hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (HCV Ab) or human immunodeficiency virus (HIV) antibody results
18. History of clinically significant cardiovascular, renal, hepatic, dermatological, chronic respiratory or GI disease, neurological or psychiatric disorder, as judged by the investigator
19. Serious adverse reaction or serious hypersensitivity to any drug
20. Known allergy or adverse reaction to dantrolene or any of the formulation excipients (macrogol, hydroxypropylbetadex, mannitol)
21. Presence or history of clinically significant allergy requiring treatment, as judged by the investigator. Hay fever is allowed unless it is active.
22. Donation of blood or plasma within the previous 3 months or loss of greater than 400 mL of blood
23. Subjects who are taking, or have taken, any prescribed or over-the-counter drug or herbal remedies (other than up to 4 g of paracetamol per day and HRT) in the 14 days before IMP administration. Exceptions may apply on a case by case basis, if considered not to interfere with the objectives of the study, as determined by the investigator.
24. Evidence of significant airway restriction or obstruction as assessed by spirometry at screening e.g. forced expiratory volume in 1 second (FEV1) <80% predicted or forced vital capacity (FVC) <80% predicted, FEV1/FVC <0.7 (70%) at screening.
25. Subjects with symptoms of or history of muscle disorder or scoliosis.
26. Failure to satisfy the investigator of fitness to participate for any other reason

Date of first enrolment
01/04/2021

Date of final enrolment
13/07/2021

Locations

Countries of recruitment
United Kingdom

England

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

Sponsor information

Organisation
Norgine, Ltd

Funder(s)

Funder type
Industry

Funder Name
Norgine

Alternative Name(s)
Norgine Ltd., Norgine Limited, Norgine Ltd, Norgine B.V., Norgine BV

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
Netherlands

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