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Study to compare the pharmacokinetics, safety and tolerability of the pediatric and adult branaplam formulation in healthy adults and the effect of food on the latter

Submission date
11/02/2022

Recruitment status
No longer recruiting

Registration date
08/04/2022

Overall study status
Completed

Last Edited
20/10/2022

Condition category
Nervous System Diseases

[X] 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 a new recipe of the test medicine, branaplam, for the potential treatment of Huntington's disease, a genetic condition that affects the nerves and how people move. The test medicine has been previously developed for a disease that affects nerves in infants and children called spinal muscular atrophy and has been used in previous clinical trials in a recipe that is suitable for children. The new recipe has been developed to be suitable for adults. This is a two-part healthy volunteer study. Part 1 consists of two periods and will compare the levels of test medicine in the blood when given as the new adult recipe or the existing pediatric recipe. Part 2 consists of two periods and will look at the effect of food on how the new adult recipe of the test medicine is taken up by the body. How safe and well tolerated the test medicine is will also be assessed in both study parts.

Who can participate?
Male and non-pregnant, non-lactating female healthy volunteers aged between 18 and 60 years

What does the study involve?
In Part 1, 16 volunteers will receive an oral dose of the pediatric recipe in one period and the new adult recipe in another period, both when in a fasted state. In Part 2, 16 volunteers will receive an oral dose of the adult recipe of the test medicine in a fed state in one period and in a fasted state in another period. Volunteers will be discharged from the clinical unit on Day 5 and will return to the clinic for three return visits on Day 8, Day 11 and Day 15 of each period. Volunteers will also receive a follow-up phone call 30 days after the final dose. Blood and urine samples will be taken throughout the study for analysis of the test medicine and for their safety. In both study parts, volunteers are expected to be involved in this study for about 13 weeks from screening to the follow-up call.

What are the possible benefits and risks of participating?
The participants will get no medical benefits. There is always a risk that the stipend in healthy

volunteer studies could represent coercion. The time spent in the clinic, travel, inconvenience and other expenses factor in calculating the stipend. Perception of risk is not considered in this calculation. When investigating new medicines there is always a risk of unexpected side effects and occasionally allergic reactions. Volunteers will be closely monitored during the study. Volunteers may experience side effects from the test medicine in this study. Full information on possible side effects is provided to volunteers in the Participant Information Sheet and Informed Consent Forms. There will be an extended period of fasting for the volunteers taking part in this study. To ensure an adequate fluid intake, the volunteers will be allowed fluids up to 2 hours before and 2 hours after dosing and will be monitored for signs of dehydration and fatigue. Blood samples will be collected during the study. Collection of these samples can cause soreness and bruising of the arms but these problems usually clear up within a few days to a few weeks. ECG stickers on volunteers' chests and limbs may cause some local irritation and may be uncomfortable to remove but volunteers will be closely monitored to ensure any local irritation does not persist.

Where is the study run from?
Novartis (Switzerland)

When is the study starting and how long is it expected to run for?
February 2022 to October 2022

Who is funding the study?
Novartis (Switzerland)

Who is the main contact?
Novartis Pharma AG Clinical Trial Information Desk
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Contact information

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Scientific

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Additional identifiers

EudraCT/CTIS number
2021-000298-10

IRAS number
1004936

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CLMI070A02104, IRAS 1004936

Study information

Scientific Title
Randomized, single-dose, open-label, two-part, two-period, cross-over study to compare the pharmacokinetics, safety and tolerability of the pediatric and adult formulation of branaplam and to investigate the adult formulation in fed and fasted state in healthy participants

Acronym
QSC205070

Study objectives
Part 1: to determine the relative BA of the adult formulation of branaplam with reference to the pediatric formulation administered to healthy participants as single branaplam doses of 112 mg

each under fasting conditions.
Part 2: to investigate the effect of food on the pharmacokinetics (PK) of the adult formulation of branaplam administered to healthy participants as single branaplam doses.

1. To determine the PK profile of branaplam and its metabolite UFB112 following a single oral branaplam dose of the adult and pediatric formulations in both study parts
2. To investigate the safety and tolerability of single oral branaplam doses using the adult and pediatric formulations in both study parts

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approval pending, London Bridge Research Ethics Committee London HRA Centre (2nd Floor, 2 Redman Place, Stratford, London, E20 1JQ, UK), REC ref: 22/LO/0106

Study design
Open-label randomized single-dose two-part two-period cross-over study

Primary study design
Interventional

Secondary study design
Randomised cross over trial

Study setting(s)
Other

Study type(s)
Treatment

Participant information sheet
No participant information sheet available

Health condition(s) or problem(s) studied
Huntington's disease

Interventions
This study will be an open-label, randomized, single-dose, two-part, two-period, cross-over study in healthy participants. A total of approximately 32 participants will be recruited for the study.

Part 1 (relative bioavailability study): a two-period crossover, adult vs pediatric formulation fasted study
In Part 1, 16 volunteers will receive an oral dose of the pediatric recipe in one period and the new adult recipe in another period, both when in a fasted state.

Part 2 (food effect study): a two-period crossover, adult formulation fed vs adult formulation fasted study
In Part 2, 16 volunteers will receive an oral dose of the adult recipe of the test medicine in a fed state in one period and in a fasted state in another period.

Participants will receive a single administration of 112 mg of the study drug on up to two separate occasions. Volunteers will be discharged from the clinical unit on Day 5 and will return to the clinic for three return visits on Day 8, Day 11 and Day 15 of each period. Volunteers will also receive a follow-up phone call 30 days after the final dose. Blood and urine samples will be taken throughout the study for analysis of the test medicine and for their safety. In both study parts, volunteers are expected to be involved in this study for about 13 weeks from screening to the follow-up call.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Branaplam

Primary outcome measure
PK parameters calculated from levels of the drug in blood plasma and urine, assessed by a validated liquid chromatography-mass spectrometry (LC-MS/MS) method of samples collected on days 1, 2, 3, 4, 5, 8, 11, 15

Secondary outcome measures
Safety measures (including vital signs, ECGs, safety laboratory parameters and adverse events [AEs]) in both study parts:
1. Vital signs measured at screening, baseline, pre-dose, days 1, 2, 3, 5, 8, 11, 15
2. ECGs measured at screening, baseline, pre-dose, days 1, 2, 3, 4, 5, 11, 15
3. Safety laboratory parameters (blood/urine) measured at screening, baseline, pre-dose, days 1, 2, 3, 4, 5, 8, 11, 15
4. Adverse events measured at screening, baseline, pre-dose, days 1, 2, 3, 4, 5, 8, 11, 15

Overall study start date
09/02/2022

Completion date
03/10/2022

Eligibility

Key inclusion criteria
1. Healthy male and non-childbearing potential female participants, 18 to 60 years of age inclusive, and in good health as determined by past medical history, physical examination, vital signs, electrocardiogram, and laboratory tests at screening and baseline 1.
2. Participants must weigh at least 50 kg at screening to participate in the study, and must have a body mass index within the range of 18.0 to 30.0 kg/m^2 as measured at screening. Body mass index = body weight (kg) / [height (m)]^2.
3. At screening and baseline vital signs (systolic blood pressure, diastolic blood pressure and pulse rate) will be assessed in the supine position and again in the standing position (after at least 3 minutes in each position). Oral body temperature will also be taken with the other supine vital sign assessments. Supine vital signs must be within the following ranges at screening and

baseline 1:
3.1. Oral body temperature 35.0-37.5°C (inclusive)
3.2. Systolic blood pressure, 90-139 mmHg (inclusive)
3.3. Diastolic blood pressure, 50-89 mmHg (inclusive)
3.4. Pulse rate, 40-90 bpm (inclusive)
Participants should be excluded if their standing vital signs (relative to supine) show findings which, in the opinion of the Investigator, are associated with clinical manifestation of postural hypotension (i.e. absence of any other cause). An Investigator should carefully consider enrolling participants with either a >20 mmHg decrease in systolic blood pressure or a >10 mmHg decrease in diastolic blood pressure accompanied by a >20 bpm increase in pulse rate.

Participant type(s)
Healthy volunteer

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
32

Key exclusion criteria
1. Participants who have received any investigational medicinal product in a clinical research study within the 90 days or 5 half-lives, whichever is longer, prior to Period 1 Day 1
2. Participants who have previously been administered investigational medicinal product in this study. Participants who have taken part in Part 1 are not permitted to take part in Part 2.
3. Significant illness, which has not resolved within 2 weeks prior to initial dosing
4. Men planning to father children in the near future (next 6 months)
5. Male participant who reports having a pregnant or nursing (lactating) partner
6. Sexually active males unwilling to adhere to the contraception requirements of the study as detailed below:
6.1. A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of the investigational drug via seminal fluid to their partner
6.2. Males with partners of childbearing potential must use a condom during intercourse while taking the investigational drug and for 118 days after stopping the investigational drug (duration to cover one spermatogenesis cycle plus 5 half-lives)
6.3. Additionally, male participants with female partners of childbearing potential should also use another highly effective method of contraception. Highly effective contraception methods include:
6.3.1. Partner’s bilateral tubal occlusion
6.3.2. Male participant sterilization (vasectomy; at least 6 months prior to screening)
6.3.3. Partner’s use of oral (estrogen and progesterone; or progesterone only that inhibits ovulation), injected, or implanted hormonal methods of contraception or placement of an intrauterine device or intrauterine system, or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example, hormone vaginal ring or transdermal

hormone contraception. In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months
6.3.4. Total abstinence (when this is in line with the preferred and usual lifestyle of the participant). Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
6.3.5. Males with partners of non-childbearing potential must use a condom during intercourse while taking the investigational drug and for 28 days after stopping the investigational drug (duration to cover 5 half-lives). In addition, male participants should not donate sperm for 118 days after stopping the investigational drug.
6.4. Women of childbearing potential who report being pregnant or nursing (lactating). Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant. Women are considered not of child-bearing potential if they are post-menopausal or have had surgical bilateral salpingectomy or bilateral oophorectomy (with or without hysterectomy) or total hysterectomy at least six weeks before screening. Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age-appropriate, history of vasomotor symptoms) and serum follicle-stimulating hormone concentration of ≥40 IU/l. Follicle-stimulating hormone and luteinizing hormone testing is required of any female participant, regardless of reported reproductive/menopausal status at screening. Refer to Section 8.4.3 Pregnancy and Assessments of Fertility. Please see the protocol for a complete detailed list of exclusion criteria.

Date of first enrolment
12/04/2022

Date of final enrolment
03/09/2022

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Quotient Sciences Limited
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Sponsor information

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Sponsor type
Industry

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ROR
https://ror.org/02f9zrr09

Funder(s)

Funder type
Industry

Funder Name
Novartis Pharma

Alternative Name(s)
Novartis Deutschland GmbH, Novartis Pharma GmbH, Novartis Deutschland

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
Germany

Results and Publications

Publication and dissemination plan
1. Internal report
2. Conference presentation
3. Publication on website
4. Submission to regulatory authorities

5. Other
6. The findings of this Phase I study will be shared with the Sponsor, Novartis Pharma AG, only. As these findings are confidential due to commercial sensitivity, it is not appropriate to share the results of this study with other researchers at this time.

Intention to publish date
03/10/2023

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study will be included in the subsequent results publication

IPD sharing plan summary
Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No