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Examining the absorption of three phenylalanine-free amino acid mixtures, one of which was formulated with the Physiomimic modified-release technology, in healthy volunteers

Submission date
01/03/2019

Recruitment status
No longer recruiting

Registration date
19/03/2019

Overall study status
Completed

Last Edited
19/05/2023

Condition category
Nutritional, Metabolic, Endocrine

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background & study aims
The aim is to demonstrate that a phe-free amino acid mixture engineered with a modified-release technology (Physiomimic technology) is able to achieve an absorption profile of AAs in blood that is different from that observed with a non-engineered phe-free AA mixture (Reference product), with lower peak plasma concentrations and a prolonged absorption over time.

The product with a modified-release technology (Physiomimic technology) is Food for Special Medical Purposes (FSMP) and is intended to be used in the dietary management of PKU patients.

In PKU patients, a reduced peak plasma concentration of AAs in blood, with a prolonged absorption over time, could lead to a better utilization of AAs (with predominant anabolism versus catabolism or inhibition of catabolism); this could potentially contribute to a better control and stabilization of blood phe levels/fluctuations, thus increasing dietary phe tolerance, i. e. the quantity of phe that could be ingested through natural diet to maintain “safe” phe levels.

Who can participate?
Male and female healthy volunteers, aged 18-45 years.

What does the study involve?
All participants will receive each study product at different test day, in fasting conditions. At each test day, blood and urine samples will be collected at baseline and at specific time points, till 7 hours.
Blood samples will be analysed for AAs, insulin, glucose and blood urea nitrogen (BUN).
Urine samples will be analysed for urea, and safety parameters.

Where are the possible benefits and risks of participating?
As the study involves healthy volunteers, there is no direct health benefit as a consequence of their participation in this study. The study will provide necessary data for further researches on the Test product.

For PKU patients, the phe-free amino acid mixture engineered with a modified-release technology (Physiomimic technology) can represent a new option for the dietary management of this metabolic disease.

The overnight fast, together with food intake restriction during each test day, may cause discomfort in subjects. In addition, drawing blood may be painful. The total amount of blood taken during the whole trial from each subject will be of approximately 475 mL, corresponding to the typical amount of blood taken during a blood donation; this may cause a slight reduction in haematology variables, such as haemoglobin. These are the typical discomforts associated with kinetic trials.

Where is the study run from?
Clinical Research Services Turku (CRST), Turku, Finland

When is the study starting and how long is it expected to run for?
October 2017 - April 2019 (finalised study report)

Who is funding the study?
APR Applied Pharma Research sa, Balerna (Switzerland)

Who is the main contact?
Anna Barassi
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Study website
N/A

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
APR/MF/01/2016 - MFAP006

Study information

Scientific Title
Comparative bioavailability of amino acids after oral intake of three phenylalanine-free amino acid mixtures – one with a modified-release technology – in healthy volunteers: a randomized crossover trial

Study objectives
A phenylalanine-free amino acid mixture engineered with a modified-release technology (Physiomimic technology) [Test product] is able to achieve an absorption profile of AAs in the blood that is different from that observed with a non-engineered phe-free AA mixture (Reference product), with lower peak plasma concentrations and a prolonged absorption over time.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 01/08/2017, Ethics Committee Varsinais-Suomen sairaanhoitopiirin eettinen toimikunta (Kiinamyllynkatu 4-8, PL 52, 20521 Turku; (02) 313 0000, sähköposti kirjaamo@tyks.fi), ref: 78 /1801/2017

Study design
Randomized, controlled, single-blind, crossover, single-dose

Primary study design
Interventional

Secondary study design
Randomised cross over trial

Study setting(s)
Other

Study type(s)
Other

Participant information sheet
Not available in web format; please, use contact details to request a participant information sheet.

Health condition(s) or problem(s) studied
Phenylketonuria

Interventions
Test product = a phenylalanine-free amino acid mixture engineered with a modified-release technology (Physiomimic technology), containing 17 AAs, vitamins, minerals, other nutrients and two food additives forming the coating layer that modifies the release of the AAs from the formulation in order to guarantee a physiological absorption of AAs.

Reference product = a non-engineered phe-free AA mixture having the same qualitative and quantitative composition of the Test product in terms of AAs, vitamins, minerals, and other nutrients. It also contains the same quantity of the two food additives but they were added in the mixing process, in a way that they do not form the coating layer giving the modified release. In view of the identical quali-quantitative composition, and the absence of the coating layer, this represents the most appropriate Reference Product for the study. i.e. the best comparison for demonstrating the effect that the coating layer has on the absorption profile of AAs in healthy volunteers (primary comparison).

Product from the market = a phe-free AA mixture containing 17 AAs, vitamins, minerals and other nutrients, available from the market for the dietary management of patients with phenylketonuria or hyperphenylalaninemia. It does not have the same quali-quantitative composition of the Test and Reference products.

Casein = a milk protein.

In addition to the screening visit, the trial consists of 4 study visits corresponding to 4 test days in which the study products are given to subjects in a randomized order (1 study product in each test day). Healthy volunteers will be randomized into one of the selected order sequences (indicated as ABDC, BCAD, CDBA, DACB), based on a balanced Latin square design.
A total of 3 washout periods between test days are foreseen, each lasting from 9 to 14 days. A follow-up visit will be performed in case of out-of-range values of safety parameters (lab tests or other exams) at the last test day (or the last study visit for the subject), which are judged of clinical relevance by the Investigator.
Subjects are divided in three weight categories, and the doses of the products for oral intake are calculated as follows:

Body weight range Test Reference Product from the market Casein
55-65.4 kg 32 g 32 g 29.4 g Dose corresponding to 20 g protein
65.5-75.4 kg 37.5 g 37.5 g 34.3 g Dose corresponding to 23.3 g protein
75.5-85 kg 43 g 43 g 39.2 g Dose corresponding to 26.6 g protein

During each test day, blood and urine samples will be collected at baseline and at specific time points after the intake of the study products (until 420 min, i.e. 7 h). At 5 h (300 min) after the intake, a light snack meal is given.

Intervention Type
Other

Primary outcome measure
1. Rate of absorption will be measured using peak plasma concentration (Cmax) of essential AAs (EAAs) after oral intake.
2. Extent of absorption will be measured using the area under the concentration-time curve (AUC) for EAAs during the first 5 hours after the intake

Plasma levels of AAs will be evaluated at the following time points: 30 min before the intake, 0, and 15 min, 30 min, 45 min, 60 min, 75 min, 90 min, 120 min, 150 min, 180 min, 240 min, 300 min, 360 min and 420 min after the intake.

Secondary outcome measures
1. Rate of absorption will be determined using Cmax of Large Neutral AAs (LNAAs), Branched-chain AAs (BCAAs), and total AAs
2. Extent of absorption in the first 5 hours will be determined using AUC0-300min of LNAAs, BCAAs, and total AAs
3. Extent of absorption during 7 hours will be determined using AUC0-420min of EAAs, LNAAs, BCAAs, and total AAs.
4. Time to reach Cmax will be measured using time to peak (tmax) of EAAs, LNAAs, BCAAs, and total AAs
5. Plasma concentrations of EAAs, LNAAs, BCAAs, and total AAs will be measured at the last evaluable time point before the snack meal (C300min) and at the last evaluable time point after the snack meal (C420min)
6. Plasma levels of blood urea nitrogen (BUN) will be measured at baseline (0 min) and at 15 min, 30 min, 45 min, 60 min, 75 min, 90 min, 120 min, 150 min, 180 min, 240 min, and 300 min after the intake
7. Plasma levels of insulin will be evaluated at baseline (0 min) and at 15 min, 30 min, 45 min, 60 min, 120 min, 180 min, 240 min, 300 min after the intake
8. Plasma levels of glucose will be evaluated at baseline (0 min) and at 15 min, 30 min, 45 min, 60 min, 120 min, 180 min, 240 min, 300 min after the intake
9. Urine levels of urea will be evaluated at baseline and over a 0- to 150-min and 150- to 300-min period after the intake
10. Safety and tolerability will be determined by performing ECG, measure of vital signs and blood/urine lab test at the last visit (liver and kidney tests, serum proteins and urine parameters will be also evaluated at the end of the 1st, 2nd and 3rd test days), and by recording any adverse event throughout the whole duration of the study

Plasma levels of AAs will be evaluated at the following time points: 30 min before the intake, 0, and 15 min, 30 min, 45 min, 60 min, 75 min, 90 min, 120 min, 150 min, 180 min, 240 min, 300 min, 360 min and 420 min after the intake.

Overall study start date
01/09/2016

Completion date
30/04/2019

Eligibility

Key inclusion criteria
1. Aged 18-45 years
2. 55-85 kg

3. Body mass index (BMI) ≤ 30 kg/m2
4. Willing to consume medical nutrition products, specifically AA preparations, and to follow the dietary scheme as required by the protocol
5. Good general health status
6. Non-smokers or not current smokers.

Participant type(s)
Healthy volunteer

Age group
Adult

Lower age limit
18 Years

Upper age limit
45 Years

Sex
Both

Target number of participants
Target number of healthy volunteers: 32. 4-8 additional subjects will be screened and available for randomization, as a back-up. Drop-outs will be replaced as long as the screening /randomization process and test meal allocation are ongoing. The aim is to reach a total of 24 evaluable subjects for the primary comparison (Test versus Reference).

Total final enrolment
30

Key exclusion criteria
1. Pregnancy, lactation or planned pregnancy
2. History of clinically significant diseases or malfunctions
3. Current illnesses that could interfere with the study
4. Use of any medication that would significantly affect protein synthesis or turnover, upon the decision of the Investigator
5. Clinically significant abnormalities in screening labs
6. Any medical condition deemed to be exclusionary by the Investigator (reasoning needs to be provided)
7. Any current participation in another clinical trial involving investigational or marketed products in the 3 months prior to the inclusion in this clinical trial
8. Blood donation of ≥250 mL within the past 3 months
9. Vegetarian diet or any food allergy towards any of the ingredients in the study products or to ingredients of snack bars/meals to be administered during the study
10. Abnormal diets or substantial changes in eating habits with the past 4 weeks
11. Positive to HIV test, or Hepatitis B or C tests

Date of first enrolment
26/10/2017

Date of final enrolment

13/02/2018

Locations

Countries of recruitment
Finland

Switzerland

Study participating centre
Clinical Research Services Turku (CRST)
Itäinen Pitkäkatu 4 B
Turku
Switzerland
20520

Sponsor information

Organisation
APR Applied Pharma Research SA

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Sponsor type
Industry

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Funder(s)

Funder type
Industry

Funder Name
APR Applied Pharma Research SA

Results and Publications

Publication and dissemination plan
Data of the clinical trial are planned to be published in a peer-review journal as soon as the final study report is finalized. Data can be disseminated as abstract/poster or oral presentation in international scientific congresses.

Intention to publish date
31/03/2020

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are not expected to be made available. They will be included as appendices to the Clinical Study Report (CSR) and will be submitted to the Ethics Committee. They will be available in case an inspection from an Health Authority is foreseen.

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	02/06/2020	08/06/2020	Yes	No
Results article		14/09/2021	19/05/2023	Yes	No