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Pharmacokinetic drug-drug interaction study between oral 300 mg netupitant/0.50 mg palonosetron fixed dose combination (Akynzeo®) and oral dexamethasone to evaluate the duration of the CYP3A4 inhibition in healthy subjects

Submission date
30/05/2016

Registration date
22/06/2016

Last Edited
07/02/2019

Recruitment status
No longer recruiting

Overall study status
Completed

Condition category
Other

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

Plain English summary of protocol

Background and study aims
Cytochrome P450 3A4 (CYP3A4) is a enzyme, mainly found in the liver and intestine, that is essential for the metabolism of many medicines. Its function is to break down molecules, such as toxins or drugs so that they can be removed from the body. Dexamethasone is a steroid that is often given to cancer patients in order to help prevent nausea and vomiting. However, it also increases the effects of CYP3A4. Netupitant is another drug that can help stop the nausea and vomiting that often occurs during cancer chemotherapy. Unlike dexamethasone, it can block (inhibit) CYP3A4 activity (that is, stop the enzyme from rapidly removing drugs from the body) This study is looking at whether a single dose of netupitant can lead to dexamethasone being in the body for a longer period of time before it is removed. The main aim of the study is to investigate (in healthy volunteers) the duration of the inhibitory (blocking) effect of a single dose of Akynzeo® (netupitant/palonosetron drug) on the activity of the CYP3A4 enzyme, using dexamethasone as a probe substrate (that is, by testing the metabolism of dexamethasone in the body) for up to 10 days.

Who can participate?
Healthy men aged between 18 and 50

What does the study involve?
All participants undergo an initial medical screening. They are then randomly allocated to one of two groups. Those in group 1 are given 12 mg of dexamethasone (3 tablets of 4 mg) for the first day of the first study period and then 8 mg of dexamethasone (2 tablets of 4 mg) on days 2,3,4,6, 8 and 10. Those in group 2 are given the same dosage of dexamethasone but are also given one Akynzeo® capsule containing 300 mg of netupitant and 0.50 mg of palonosetron on day 1 of the

study period.
There is then a “washout period” of at least 35 days, where participants are not given any of the drugs to take. They then swap groups, so that those participants that were in group 1 are now in group 2 and the drug dosing repeated. This means that all participants have been treated as group 1 and group 2 participants. During the two study periods blood samples are taken to see how they are being metabolised in the body.

What are the possible benefits and risks of participating?
No specific benefits for participants are foreseen except for the medical screening. All participants are paid for their time. The risk of adverse drug reactions to Akynzeo® is expected to be very low and the risk of adverse reactions to the dexamethasone is not expected to be any worse than dexamethasone is taken on its own. Blood sampling may cause some minor discomfort to the participants.

Where is the study run from?
CROSS Research SA (Switzerland)

When is the study starting and how long is it expected to run for?
December 2014 to July 2015

Who is funding the study?
Helsinn Healthcare SA (Switzerland)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
Study CRO-PK-14-293 - Sponsor code NEPA-14-39

Study information

Scientific Title
Pharmacokinetic drug-drug interaction study between oral 300 mg netupitant/0.50 mg palonosetron fixed dose combination (Akynzeo®) and oral dexamethasone. Evaluation of the duration of the CYP3A4 inhibition in a randomized, two-period, two-sequence, crossover study in healthy subjects

Acronym
NetuPalo – dexamethasone CYP3A4 inhibition duration

Study objectives
The main aim of the study is to evaluate in healthy subjects the duration of the inhibitory effect of a single oral dose of the netupitant/palonosetron 300mg/0.50 mg fixed dose combination (NEPA FDC) on the CYP3A4 enzyme activity, using dexamethasone as a probe substrate.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Cantonal Ethic Committee, 25/03/2015, ref: 2899

Primary study design
Interventional

Study design
Open-label, randomized, 2-period, 2-sequence, crossover study

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Inhibitory effect on CYP3A4

Interventions
During the trial the following investigational medicinal products (IMPs) were administered:

1. Akynzeo , netupitant/palonosetron 300mg/0.50 mg fixed dose combination: interacting drug
2. Dexamethason 4 mg tablet: substrate

The study protocol foresaw two periods separated by a wash-out interval of at least 35 days, i.e. day 1 of period 1 and day 1 of period 2 were separated by at least 35 days.

Each subject was randomized to receive the substrate alone in period 1 and the substrate co-administered with the interacting drug in period 2 or vice versa. Therefore in each study period, all the subjects received a single dose of 12 mg of dexamethasone (3 tablets of 4 mg) on day 1, then single 8 mg doses (2 tablets of 4 mg) in the morning on days 2, 3, 4, 6, 8 and 10. According to the randomisation cross-over design, the subject received a single oral dose of Akynzeo® was given to the subjects as a single hard-gelatin capsule, containing 300 mg of netupitant and 0.50 mg of palonosetron, in the morning of day 1 in one of the 2 periods.

During the two study periods blood samples were taken to determine the PK profile of dexamethasone , netupitant and palonosetron. The primary evaluation of the end of the

netupitant inhibitory effect will be based on dexamethasone absorption (AUC) measured on days 1, 4, 6, 8 and 10 with or without the interacting drug.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
1. Netupitant/palonosetron 300 mg/0.50 mg (NEPA FDC) hard gelatin capsules (Akynzeo®) 2. Dexamethasone 4 mg tablets (Dexamethason 4 mg Jenapharm®)

Primary outcome(s)
Evaluation of the pharmacokinetic profile of oral dexamethasone on Days 1, 4, 6, 8 and 10 with and without co-administration of a single dose of NEPA FDC on Day 1

Key secondary outcome(s)
1. To describe the plasma pharmacokinetic profile of netupitant and palonosetron
2. To collect safety and tolerability data

Completion date
31/07/2015

Eligibility

Key inclusion criteria
1. Informed consent: signed written informed consent before inclusion in the study
2. Gender and age: male subject, 18-50 year old inclusive
3. Health conditions: general good health, based upon the results of the medical history, physical examination, vital signs and ECG measurements
4. Body weight: body weight ≥ 50 kg and body mass index between 18.5 and 30 kg/m2 inclusive
5. Tobacco: non-smoker or having stopped smoking and using other products containing nicotine for at least 6 months before screening
6. Hemoglobin and ferritin: 14 g/dL≤hemoglobin≤18 g/dL and ferritin>30 ng/mL measured at the screening visit
7. Vital signs: systolic blood pressure 100-139 mmHg, diastolic blood pressure 50-89 mmHg, pulse rate 50-90 bpm, measured after 5 min at rest in the sitting position
8. Full comprehension: ability to understand the nature of the study and willing to comply with the protocol requirements

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Upper age limit
50 Years

Sex
Male

Key exclusion criteria
1. Investigative drug studies: participation in any investigational trial within 3 months before the planned first study drug administration in the study
2. Netupitant studies: enrolment in a previous study of netupitant (alone or in combination with palonosetron)
3. Allergy: history of significant allergies (including asthma, food, or drug allergies), as determined by the investigator
4. Hypersensitivity: history of hypersensitivity to any of the study treatments or to any of their excipients
5. Blood donation: having significant blood losses or having donated or received blood within 90 days before the planned first study drug administration in the study or during the study
6. Medications: receiving any prescription or over-the-counter medications or vitamins or herbal supplements within 21 days before the planned first study drug administration in the study and during the whole study
7. CYP3A4 inducers and inhibitors: use of any inducer or inhibitor of CYP3A4 enzymes within 28 days before the planned first study drug administration in the study and during the whole study
8. Drug: history of drug abuse
9. Alcohol: history of alcohol abuse [>2 drinks/day for males, defined according to the USDA Dietary Guidelines 2010]
10. Alcohol test: positive alcohol breath test at the screening visit or Day -1 of each treatment period
11. Clinical conditions: any clinical condition or prior therapy that, in the investigator’s opinion, would make the subject unsuitable for the study or unable to comply with the dosing requirements
12. Fever and infections: febrile or infectious illness within 7 days before the planned first study drug administration in each treatment period
13. Malabsorption: any condition which might interfere with the absorption of the investigational medicinal products (e.g. cholecystectomy, cholecystolithiasis)
14. Contraindications: known contraindication to NK-1 receptor antagonists and/or 5-HT3 receptor antagonists and/or dexamethasone
15. Xanthines: excess in consumption of xanthine-containing food or beverages (i.e., more than 5 cups of coffee or equivalent per day) within 48 hours before the planned first study drug administration in the study and during the whole study (including wash-out period)
16. Diet and life style: intake of alcohol or food (as grapefruit juice) known to interfere with cytochrome P450 (CYP) within 168 hours (1 week) before the planned first study drug administration in the study and during the whole study
17. Laboratory analyses: clinically significant abnormal laboratory values of hematology, clinical blood chemistry or urine analysis (dipstick) indicative of physical illness
18. Creatinine: creatinine clearance, calculated using the Cockcroft-Gault formula, >1.5 times the upper normal limit
19. Virology: positive laboratory test results for hepatitis B surface antigen, hepatitis C virus antibodies or human immunodeficiency virus

20. Abuse drug test: positive urine drug test results (dipstick test for cocaine, amphetamine, methamphetamine, cannabinoids, opiates and ecstasy) at the screening visit or Day -1 of each treatment period
21. Electrocardiogram (ECG) 12-leads (supine position): clinically significant abnormalities
22. Physical findings: clinically significant abnormal physical findings which could interfere with the objective of the study

Date of first enrolment
18/05/2015

Date of final enrolment
29/05/2015

Locations

Countries of recruitment
Switzerland

Study participating centre
CROSS Research SA
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Arzo
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6864

Sponsor information

Organisation
Helsinn Healthcare SA

ROR
https://ror.org/01kdzkq48

Funder(s)

Funder type
Industry

Funder Name
Helsinn Healthcare SA

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results		07/02/2019	07/02/2019	No	No