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Comparing the fraction of Vitamin D3 that reaches the blood circulation in healthy volunteers after a single dose of either a marketed liquid medication or a new form of the medication that is dissolvable in the mouth

Submission date
18/11/2020

Recruitment status
No longer recruiting

Registration date
27/11/2020

Overall study status
Completed

Last Edited
07/12/2022

Condition category
Nutritional, Metabolic, Endocrine

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

Plain English summary of protocol

Background and study aims
Vitamin D3 is very important for health because strengthens the bones, helps prevent autoimmune diseases, regulates neuromuscular function and helps fight the symptoms of depression. The new orodispersible formulation developed by IBSA for the present study dissolves and/or disintegrates rapidly when placed in the mouth without drinking or chewing, providing a valuable alternative to the already marketed drug products for vitamin D supplementation.

The main aim of this study is to compare the amount of the active substance of a new vitamin D3 formulation that reaches the blood flow compared to a reference formulation in healthy subjects.

Who can participate?
Healthy people aged 40-70 years old, were able to participate. Participants had to comprehend the full nature and purpose of the study, including possible risks and side effects and co-operate with the investigator to comply with the requirements of the entire study. Women of childbearing potential were required to use at least one reliable method of contraception.

What does the study involve?
Study participants will be randomly allocated to one of three groups to receive a single dose of the study drug (IBSA Vitamin D3 orodispersible film) by mouth or the reference drug (a liquid taken by mouth):
1. The Tfast group were administered a single dose of the study drug under fasting conditions
2. The Tfed group were administered a single dose of the study drug under fed conditions
3. The Rfed group were administered a single dose of the reference drug under fed conditions

The study drug being tested is not yet available on the market in Switzerland, and should therefore be considered a trial product whereas the reference formulation is already on the market. Participants will have blood samples taken, and vital parameters recorded at regular intervals.

In addition, a full physical examination (body weight, height, vital signs, physical abnormalities) and laboratory parameters (measured on blood and urine samples, as applicable) will be performed at the screening and final visit (or, if participants leave the trial before the final visit, at the point of participation being terminated early).

What are the possible benefits and risks of participating?
Participating in this study is not expected to bring any direct benefit to participants, with the exception of the medical tests that will be performed during the study. Vitamin D supplementation is safe. No toxicity is expected at the dose foreseen in the present study, which will be administered once to each volunteer. However, as with all products, the appearance of allergic reactions or side effects that are known or not yet known cannot be ruled out.

Where is the study run from?
The CROSS Research S.A. Phase I Unit Clinical Centre (Switzerland)

When is the study starting and how long is it expected to run for?
From May 2019 to November 2019.

Who is funding the study?
IBSA Institut Biochimique S.A. (Switzerland)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
19CH-D3f01

Study information

Scientific Title
Vitamin D3 bioavailability comparison between a marketed oral solution and a new orodispersible film in healthy volunteers

Study objectives
To compare the bioavailability of vitamin D3 (measured as plasma calcifediol, 25-hydroxyvitamin D) after single oral dose of IBSA Vitamin D3 25000 I.U. orodispersible film versus the marketed reference DIBASE® under fed conditions in healthy adult male and female subjects.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 13/06/2019, Canton Ticino Ethics Commitee (c/o Ufficio di sanità, Via Orico 5, 6501Bellinzona, Switzerland; +41(0)91 814 30 57; beatrice.giberti-gai@ti.ch), ref: 2019-00932 / CE 3479

Primary study design
Interventional

Study design
Single-dose randomized parallel-group open-label bioavailability study

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Vitamin D deficiency

Interventions
The first screening visit will take place between Day -21 and Day -2. Study participants will be randomly allocated, according to a randomised parallel group design (1:1:1), to one treatment according to the randomisation list, computer-generated by the Biometry Unit of the Contract Research Organisation (CRO) and supplied to the study site before study start. This is an open label study. Subjects will be randomised on Day -1, according to their randomisation number, and will be allocated to one of the following three groups, to receive either a single dose of test (T) (IBSA Vitamin D3 25000 I.U. orodispersible film) or the reference (R) (DIBASE®, oral solution) treatments:
1. The Tfast group were administered a single dose of T under fasting conditions
2. The Tfed group were administered a single dose of T under fed conditions
3. The Rfed group were administered a single dose of R under fed conditions

Both test and reference treatments will be orally administered. Before administration, all the subjects will wet their mouth by swallowing 20 ml of still mineral water. Tfast subjects will receive the test product under prolonged fasting conditions (from 10 h pre-dose to 5 h post-dose), while Tfed and Rfed subjects will receive the IMPs 30 min after having started to eat a light breakfast. Rfed subjects will drink the contents of 1 vial of reference treatment immediately on opening. Tfast and Tfed subjects will open 1 sachet containing one orodispersible film of test treatment and its contents will be immediately placed on their tongue, allowing it to dissolve without chewing.

Participants will have blood samples taken, and vital parameters recorded at regular intervals. Blood samples will be taken at -12, -1, and 0 h, 15 and 30 min, and 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 144, 312, 480 and 648 h. Subjects will attend 8 visits for assessment, Visit 3 will take place on one of Days 1-3, Visit 4 on Day 4, Visit 5 on Day 7, Visit 6 on Day 14, Visit 7 on Day 21, and Visit 8 on Day 28. In the case of early discontinuation, discontinued subjects will undergo an early termination visit (ETV).

Subjects are weighed (kg) lightly clothed without shoes to record body weight at screening and final visit or the early termination visit (ETV). Height is measured at screening only. Body Mass Index (BMI) is calculated as weight [kg]/(height [m] x height [m]) at screening and final visit/ETV. Vital signs (blood pressure [mmHg], heart rate [bpm]) are measured by the investigator after 5 min at rest in sitting position at screening, -1 days and final visit/ETV. A 12-Lead ECGs will be performed in the supine position at screening.

The following laboratory analysis will be performed:
1. Haematology, blood chemistry, serum virology, and urine analysis at the screening visit
2. A urine drug test and a serum pregnancy test at the screening visit and at the entrance of each study period
3. Haematology, blood chemistry, and urine analysis at the final visit/ETV

Subjects are asked about the occurrence of adverse events (AEs) from the Informed Consent (IC) signature to the study end. Additionally, any clinically significant vital sign or laboratory value is reported as AE. AEs are coded by System Organ Class (SOC) and Preferred Term (PT), using the Medical Dictionary for Regulatory Activities (MedDRA). AEs are classified as pre-treatment AEs (PTAEs) and Treatment-Emergent AEs (TEAEs), according to the period of occurrence, as follows:
1. PTAEs include all AEs occurring after IC signature by the enrolled subject but before the first dose of IMP
2. TEAEs include all AEs occurring or worsening after the administration of the first dose of IMP

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
colecalciferol (vitamin D3), IBSA Vitamin D3 25000 I.U. orodispersible film

Primary outcome(s)
1. Bioavailability of vitamin D3 after a single oral dose of Test (T) or marketed reference (R), under fed conditions, measured as maximum serum concentration (Cmax) and area under the plasma drug concentration-time curve (AUC0-t) of for plasma calcifediol (25(OH)D3) using a fully

validated Liquid Chromatography with tandem mass spectrometry (LC-MS-MS) method, with a lower quantification limit of 1 ng/ml, on blood samples taken at -12, -1, and 0 h, 15 and 30 min, and 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 144, 312, 480 and 648 h

Key secondary outcome(s)

1. Maximum serum concentration (Cmax) and area under the plasma drug concentration-time curve (AUC0-t) of for plasma calcifediol (25(OH)D3) after a single dose administration of T under fasting and fed conditions measured using a fully validated Liquid Chromatography with tandem mass spectrometry (LC-MS-MS) method, with a lower quantification limit of 1 ng/ml, on blood samples taken at -12, -1, and 0 h, 15 and 30 min, and 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 144, 312, 480 and 648 h
2. Pharmacokinetic (PK) profile of 25(OH)D3 after a single dose administration of T and R under fed conditions measured using a fully validated Liquid Chromatography with tandem mass spectrometry (LC-MS-MS) method, with a lower quantification limit of 1 ng/ml, on blood samples taken at -12, -1, and 0 h, 15 and 30 min, and 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 144, 312, 480 and 648 h
3. PK profile of 25(OH)D3 after a single dose administration of T under fasting conditions measured using a fully validated Liquid Chromatography with tandem mass spectrometry (LC-MS-MS) method, with a lower quantification limit of 1 ng/ml, on blood samples taken at -12, -1, and 0 h, 15 and 30 min, and 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 144, 312, 480 and 648 h
4. Safety and tolerability of Vitamin D3 will be evaluated during the study by the number of adverse events (AEs) reported throughout the study duration and measured using:
4.1. Blood and urine samples for haematology, blood chemistry, and urine analysis at the screening visit and final visit/ETV
4.2. Body weight at the screening visit and final visit/ETV and height at the screening visit to calculate Body Mass Index (BMI) at the screening visit and final visit/ETV
4.3. Vital signs (blood pressure [mmHg], heart rate [bpm]) at the screening visit, -1 days, and final visit/ETV
4.4. 12-Lead electrocardiogram at the screening visit
5. Palatability and ease of use of the test product measured using the score given by the subjects to the following parameters: taste, intensity of taste, aftertaste, mouth feel and ease of use measured immediately after administration

Completion date

22/11/2019

Eligibility

Key inclusion criteria

1. Signed written informed consent before inclusion in the study
2. Aged 40-70 years inclusive
3. Body Mass Index (BMI) 20-29 kg/m² inclusive
4. Systolic blood pressure between 100-139 mmHg, diastolic blood pressure between 50-89 mmHg, heart rate between 50-90 bpm (all measured after 5 min at rest in the sitting position)
5. Ability to comprehend the full nature and purpose of the study, including possible risks and side effects, and to co-operate with the investigator, and to comply with the requirements of the entire study
6. Women of childbearing potential must be using at least one of the following reliable methods of contraception:
6.1. Hormonal oral, implantable, transdermal, or injectable contraceptives for at least 2 months before the screening visit

6.2. A non-hormonal intrauterine device or female condom with spermicide or contraceptive sponge with spermicide or diaphragm with spermicide or cervical cap with spermicide for at least 2 months before the screening visit
6.3. A male sexual partner who agrees to use a male condom with spermicide
6.4. A sterile sexual partner
7. Female participants of non-child-bearing potential or in post-menopausal status for at least one year will be admitted
8. For all women, pregnancy test result must be negative at screening and Day -1

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Total final enrolment
48

Key exclusion criteria
1. Clinically significant abnormalities on 12-lead (supine position) electrocardiogram (ECG)
2. Clinically significant abnormal physical findings which could interfere with the objectives of the study
3. Clinically significant abnormal laboratory values indicative of physical illness, especially hypercalcemia and hypercalciuria
4. Ascertained or presumptive hypersensitivity to the active principle and/or formulations' ingredients, history of anaphylaxis to drugs, or history of allergic reactions in general which the investigator considers may affect the outcome of the study
5. Significant history of renal, hepatic, gastrointestinal, cardiovascular, respiratory, skin, haematological, endocrine, or neurological diseases that may interfere with the aim of the study, especially sarcoidosis, kidney failure, nephrolithiasis, nephrocalcinosis, or liver failure
6. Medications including over the counter (OTC) medications, herbal remedies, and supplements, especially those containing calcium, magnesium or vitamin D, for 2 weeks before the start of the study. Hormonal contraceptives and hormonal replacement therapy for women will be allowed.
7. Participation in the evaluation of any investigational product within the 3 months of the first day of this study. The 3-month interval is calculated as the time between the first calendar day of the month that follows the last visit of the previous study and the first day of the present study.
8. Blood donations within the 3 months of the first day of this study
9. History of drug, alcohol (>1 drink/day for women and >2 drinks/day for men), caffeine (>5 cups /day of coffee or tea) or tobacco abuse (≥10 cigarettes/day)
10. Positive result at the drug test at screening or Day -1
11. Positive alcohol breath test at Day -1
12. Abnormal diets (<1600 or >3500 kcal/day), substantial changes in eating habits within 4 weeks of the first day of this study, vegetarian diet; or high vitamin D and calcium dietary intake within 4 weeks of the first day of this study

13. Exposure to strong sunlight or UV sources within 2 weeks of the first day of this study
14. Pregnant or lactating women or a positive or missing pregnancy test at screening or Day -1

Date of first enrolment
24/09/2019

Date of final enrolment
07/10/2019

Locations

Countries of recruitment
Italy

Switzerland

Study participating centre
CROSS Research S.A.
Phase I Unit
Via F.A. Giorgioli 14
Arzo
Switzerland
6864

Sponsor information

Organisation
IBSA Institut Biochimique (Switzerland)

ROR
https://ror.org/051tj3a26

Funder(s)

Funder type
Industry

Funder Name
IBSA Institut Biochimique S.A.

Results and Publications

Individual participant data (IPD) sharing plan

The data sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary

Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		16/01/2022	17/01/2022	Yes	No
Basic results		08/09/2021	08/09/2021	No	No