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A study to assess the amount of active ingredient that reaches the blood circulation after administration in healthy men and women under fasting conditions of a new antianxiety, sedative, and anticonvulsant mouth-dissolvable drug in comparison to the marketed tablets of Tavor®

Submission date 20/12/2022	**Recruitment status** No longer recruiting	[_] Prospectively registered [X] Protocol
Registration date 10/01/2023	**Overall study status** Completed	[_] Statistical analysis plan [X] Results
Last Edited 29/03/2023	**Condition category** Other	[_] Individual participant data

Plain English summary of protocol

Background and study aims

A new orodispersible film containing lorazepam, an active ingredient commonly prescribed for a wide range of anxiety-related conditions, has been developed to provide an easy-to-take and rapidly dissolvable alternative to the marketed oral products for the short-term symptomatic treatment of anxiety and insomnia. This study is designed to investigate the amount of lorazepam that reaches the blood circulation after administration of the new lorazepam orodispersible film versus each of two reference products, i.e., Tavor® 2.5 mg tablets and Tavor® 2.5 mg orodispersible tablets, when administered to healthy men and women under fasting conditions.

Who can participate?

Healthy men and women aged 18-55 years can participate. They must 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.

What does the study involve?

The study will be conducted at the CROSS Research S.A. Phase I Unit Clinical Centre, in Arzo, Switzerland. Study participants will receive a single dose of Lorazepam IBSA 2.5 mg orodispersible film, a single dose of Tavor® 2.5 mg tablets and a single dose of Tavor® 2.5 mg orodispersible tablets in 3 study periods, according to a 3-way cross-over randomised design, with a wash-out interval of at least 7 days between consecutive administrations. Participants will have blood samples taken and vital parameters recorded at regular intervals.

What are the possible benefits and risks of participating?
Participating in this study will not bring any direct benefit to participants, with the exception of the medical tests that will be performed during it. Lorazepam is a well-known active substance with established efficacy and tolerability. The formulation under investigation, Lorazepam IBSA 2.5 mg orodispersible film, will be administered to men and women the first time in this clinical study. In any case, lorazepam 2.5 mg orodispersible formulations are already marketed and undesirable effects known (above all, daytime drowsiness, sedation and asthenia). Overall, lorazepam administered as a single oral dose to healthy subjects is safe and well tolerated. 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 study will be conducted at the CROSS Research S.A. Phase I Unit Clinical Centre, in Arzo, Switzerland.

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

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

Who is the main contact?
Dr. Milko Radicioni, clinic@croalliance.com

Contact information

Type(s)
Scientific

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Protocol serial number
22CH-Lrz05

Study information

Scientific Title
Comparative bioavailability study of a new Lorazepam IBSA 2.5 mg orodispersible film vs. Tavor® 2.5 mg tablets and Tavor® 2.5 mg orodispersible tablets in healthy volunteers under fasting conditions

Study objectives
To compare the bioavailability of lorazepam after a single dose of Lorazepam IBSA 2.5 mg orodispersible film versus each of two reference products, i.e., Tavor® 2.5 mg tablets and Tavor® 2.5 mg orodispersible tablets, when administered to healthy men and women under fasting conditions.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 08/06/2022, Canton Ticino Ethics Committee (c/o Ufficio di Sanità, Via Orico 5, 6501 Bellinzona, Switzerland; +41(0)91.814.30.57; beatrice.giberti-gai@ti.ch), ref: 2022-00923 CE 4109

Primary study design
Interventional

Study design
Single centre single dose open-label randomized 3-way cross-over pilot bioavailability study

Study type(s)
Other

Health condition(s) or problem(s) studied
Lorazepam with antianxiety, sedative and anticonvulsant effects

Interventions
For each subject, a single dose of Lorazepam IBSA 2.5 mg orodispersible film, a single dose of Tavor® 2.5 mg tablets and a single dose of Tavor® 2.5 mg orodispersible tablets will be administered under fasting conditions in 3 study periods, according to a 3-way cross-over randomised design, with a wash-out interval of at least 7 days between consecutive administrations.
The investigational medicinal products will be orally administered under fasting conditions on Day 1 of each study period at 08:00±1h as follows:
- one orodispersible film of Lorazepam IBSA 2.5 mg without water
- one tablet of Tavor® 2.5 mg with 150 mL of still mineral water
- one orodispersible tablet of Tavor® 2.5 mg without water.

The Investigator or deputy will take the orodispersible products out of packaging just before the administration.
To avoid inadvertent breakages of Lorazepam IBSA 2.5 mg orodispersible film, the Investigator or deputy shall:
1. take the envelope and hold it with the side not sealed facing up
2. gently peel both parts of the envelope and then hold each between his/her thumb and index fingers using one hand for each part
3. carefully tear both parts of the envelope in opposite directions until they will be separated. The oral film will be visible and placed on one of the separated envelope parts.

To avoid inadvertent breakages of Tavor® 2.5 mg orodispersible tablet, the Investigator or deputy shall:
1. lift the lateral tab
2. remove the tab
3. take out the orodispersible tablet by pressing on the blister pouch.
The Investigator or deputy will place each of the two orodispersible products directly on the subject's tongue. The Investigator will wear gloves during the administration procedure. Subjects will let the orodispersible product completely dissolve in their mouth. It must not be swallowed whole and must not be chewed or broken. The subject will be allowed to swallow saliva as the orodispersible product dissolves in the mouth. In details, once the subject feels that the orodispersible product has completely dissolved, he/she will inform the Investigator who will inspect the subject’s mouth and verify the complete dissolution in the mouth. If the subject does not inform the Investigator within 2 minutes of the administration, his/her mouth will be checked by the Investigator at 2 and again at 3 minutes, if needed. If, upon inspection at 2 or 3 minutes, the orodispersible product is already dissolved, the time of mouth check will be recorded as dissolution end time. If the orodispersible product is not completely dissolved within 3 min, the subjects will be allowed to swallow without water. In this case, the dissolution end time will be considered as not applicable. The exact date and time of orodispersible product administration (defined as the time at which the orodispersible product is placed on the subject’ s tongue by the Investigator or deputy) and the time of complete dissolution of the orodispersible product (no residues present at inspection of the oral cavity by the Investigator or deputy) will be recorded. Dissolution times will be collected in specific source documents and subjects’ case report forms. The occurrence of inadvertent chewing and/or breaking and/or swallowing will be recorded.
For the administration of Tavor® 2.5 mg tablet, the subject will swallow the tablet with 150 mL of still mineral water. The tablet must be swallowed whole and must not be chewed or broken. Product administration date and time will be recorded as well.

Intervention Type
Drug

Phase
Phase I

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

Primary outcome(s)
Rate (Cmax) and extent (AUC0-t and AUC0-inf, if feasible) of lorazepam absorption in plasma measured from plasma samples taken at pre-dose (0) and 0.5 (30 min), 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 36, 48 and 72 h post-dose after administration of each of the three treatments (Lorazepam IBSA 2.5 mg orodispersible film, Tavor® 2.5 mg tablets and Tavor® 2.5 mg orodispersible tablets) under fasting conditions

Key secondary outcome(s)
1. Time to peak (tmax), relative bioavailability (Frel) and, if feasible, elimination half-life (t1/2) and terminal elimination rate constant (λz) of plasma lorazepam measured from plasma samples taken at pre-dose (0) and 0.5 (30 min), 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 36, 48 and 72 h post-dose after administration of each of the three treatments (Lorazepam IBSA 2.5 mg orodispersible film, Tavor® 2.5 mg tablets and Tavor® 2.5 mg orodispersible tablets) under fasting conditions

2. All adverse events occurring after informed consent signature but before the first dose of investigational medicinal product (PTAEs), all adverse events occurring or worsening after the first dose of investigational medicinal product (TEAEs), vital signs (blood pressure and heart rate, measured at screening visit, on Day -1 of each study period, on Days 1-4 of each study period at pre-dose (0), 1.5, 3, 24, 48 and 72 h post-dose and at early termination visit [ETV] as applicable), body weight (measured at screening and final visit/ETV as applicable), physical examinations (performed at screening and final visit/ETV as applicable), clinical laboratory parameters (haematology, blood chemistry and urine analysis performed at screening and final visit/ETV as applicable; virology performed at screening; urine drug test performed at screening; a serum pregnancy test at screening; urine pregnancy test at the entrance of each study period), ECG (performed at screening and final visit/ETV as applicable).

Completion date
05/10/2022

Eligibility

Key inclusion criteria
1. Informed consent: signed written informed consent before inclusion in the study
2. Sex and Age: men and women, 18-55 years old inclusive
3. Body Mass Index: 18.5-30 kg/m² inclusive
4. Vital signs: systolic blood pressure 100-139 mmHg, diastolic blood pressure 50-89 mmHg, heart rate 50-90 bpm, measured after 5 min at rest in the sitting position
5. Full comprehension: ability to comprehend the full nature and purpose of the study, including possible risks and side effects; ability to co-operate with the Investigator and to comply with the requirements of the entire study
6. Contraception and fertility (women only): women of child-bearing potential must be using at least one of the following reliable methods of contraception:
a. 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
b. A male sexual partner who agrees to use a male condom with spermicide
c. A sterile sexual partner
Female participants of non-child-bearing potential or in post-menopausal status for at least 1 year will be admitted. 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

Lower age limit
18 Years

Upper age limit
55 Years

Sex
All

Total final enrolment
18

Key exclusion criteria
Subjects meeting any of these criteria will not be enrolled in the study:
1. Electrocardiogram (12-lead ECG in supine position): clinically significant abnormalities
2. Physical findings: clinically significant abnormal physical findings which could interfere with the objectives of the study; presence of mouth lesions or any other oral mucosa alteration; presence or history (within 28 days) of any tongue piercings; presence of any partials, braces or dentures
3. Laboratory analyses: clinically significant abnormal laboratory values indicative of physical illness
4. Allergy: ascertained or presumptive hypersensitivity to the active principle or formulations' ingredients or both; history of anaphylaxis to drugs or allergic reactions in general, which the Investigator considers may affect the outcome of the study
5. Diseases: significant history of renal, hepatic, gastrointestinal, cardiovascular, respiratory, skin, haematological, endocrine, immunological or neurological diseases that may interfere with the aim of the study
6. Medications: medications, including over the counter medications and herbal remedies for 2 weeks before the start of the study. Hormonal contraceptives for women will not be allowed
7. Investigative drug studies: participation in the evaluation of any investigational product for 3 months before 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 donation: blood donations for 3 months before this study
9. Drug, alcohol, caffeine, tobacco: history of drug, alcohol [>1 drink/day for women and >2 drinks/day for men, defined according to the USDA Dietary Guidelines 2020-2025], caffeine (>5 cups coffee/tea/day) or tobacco abuse (10 cigarettes/day)
10. Drug test: positive result at the drug test at screening
11. Alcohol test: positive alcohol breath test at Day -1
12. Diet: abnormal diets (<1600 or >3500 kcal/day) or substantial changes in eating habits in the 4 weeks before this study; vegetarians
13. Pregnancy (women only): positive or missing pregnancy test at screening or Day -1, pregnant or lactating women.

Date of first enrolment
23/08/2022

Date of final enrolment
25/08/2022

Locations

Countries of recruitment
Switzerland

Study participating centre
CROSS Research S.A.
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 current data sharing plans for this study are unknown and will be available at a later date.

IPD sharing plan summary
Stored in non-publicly available repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results		29/03/2023	29/03/2023	No	No
Protocol file	version 1.0	16/05/2022	22/12/2022	No	No