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A phase Ib study to evaluate the Pharmacodynamic properties of topically applied TAR-0520 gel in healthy subjects

Submission date
27/03/2024

Recruitment status
No longer recruiting

Registration date
05/04/2024

Overall study status
Completed

Last Edited
20/06/2024

Condition category
Other

[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 TAR-0520 gel, containing Brimonidine tartrate, is developed to address three skin issues from cancer treatments: Radiation-induced Dermatitis (RID) after breast cancer surgery, EGFR induced folliculitis in colon cancer patients on EGFR inhibitors, and Hand-Foot Syndrome (HFS) from capecitabine. Brimonidine, known for treating glaucoma and facial redness in rosacea, constricts superficial blood vessels when applied to the skin, limiting systemic absorption.

Its pharmacological actions support its use through three mechanisms:
1. Constriction reduces blood flow, limiting drug access to the skin.
2. Decreased oxygen levels in the skin reduce Reactive Oxygen Species (ROS) production, lessening oxidative stress.
3. Reduced vessel permeability decreases inflammatory substance leakage, diminishing inflammation.

Studies, such as those by Lacouture et al. on EGFR-induced folliculitis, Arne Gerber's reports on HFS improvement, and Cleary et al.'s findings on reducing radiodermatitis severity, validate these mechanisms. By targeting these pathways, TAR-0520 gel offers localized relief for cancer treatment-related skin issues.

Who can participate?
Healthy volunteers - Male and female 18-59 years old

What does the study involve?
This study is focused on investigating the effects of TAR-0520 gel at two different concentrations (1.5% or 1%) applied to small areas of skin on the chest and face. It's being conducted as a Phase 1b trial with healthy adult participants, and it will take about 8 weeks to complete, including a 4-week screening phase and a 4-week evaluation period.

During the first part of the study, the TAR-520 gel will be applied daily (except weekends) to four small skin areas for 3 weeks (totaling 15 applications). After a short break of either 4 or 7 days (determined randomly), a single application of TAR-0520 will be applied to the same areas.

The initial phase aims to understand how TAR-0520 works, assess its local tolerance, and detect any potential decrease in its ability to constrict blood vessels over time. The second phase will investigate how taking a break from treatment affects its ability to constrict blood vessels.

What are the possible benefits and risks of participating?
This project involves repurposing a drug called brimonidine tartrate, which has been approved since 1996. Through extensive testing, no safety concerns were found in nonclinical studies, including long-term tests on animals using topical formulations containing up to 2.0% of brimonidine tartrate. There were no indications of skin cancer or other adverse effects.

Clinical data from the development of Mirvaso® gel (Brimonidine tartrate 0.5%) further confirmed the safety of using brimonidine tartrate topically, with only minor local side effects observed and no long-term safety issues. Blood tests also showed no significant changes in subjects treated with brimonidine tartrate gel.

Testing of TAR-0520 gel, containing 0.5 to 1.5% brimonidine tartrate, on the skin of rats showed it was well tolerated without causing irritation. This was also confirmed in a 13-week study on minipigs, where no signs of irritation or sensitization were observed.

The amount of brimonidine absorbed into the bloodstream from topical application is expected to be similar to that of already marketed products. Studies showed that systemic exposure in humans from applying 2 g of brimonidine 0.5% gel was lower compared to using one drop of 0.2% brimonidine ophthalmic solution in each eye three times a day. Additionally, a 21-day rat study with TAR-0520 0.5% gel did not show significantly higher exposure compared to Mirvaso® gel (Brimonidine 0.5%).

Where is the study run from?
CIDP (Mauritius)

When is the study starting and how long is it expected to run for?
March 2024 to August 2024

Who is funding the study?
Tarian Pharma (France)

Who is the main contact?
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Contact information

Type(s)
Public, Scientific, Principal investigator

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Additional identifiers

Protocol serial number
2324CMCL096

Study information

Scientific Title
Pharmacodynamic effects of TAR-0520 gel applied topically in healthy participants

Study objectives
The hypothesis is that reducing the skin capillary blood flow in a skin area which is known to be susceptible to the toxicity of a given chemotherapy, will decrease the skin bioavailability of the said chemotherapy to a quantity that would be below the toxic level for the skin. To achieve the best protection, a strong and long vasoconstriction effect is considered as the main driver for optimal prevention.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 28/05/2024, Clinical Research Regulatory Council (Atchia Building, Suffren Street, Port-Louis, 11405, Mauritius; +230 59439503; crrc@govmu.org), ref: 2324CMCL096

Primary study design
Interventional

Study design
Interventional randomized controlled trial

Study type(s)
Efficacy

Health condition(s) or problem(s) studied
Healthy participants

Interventions
This is a monocentric, investigator-blinded, pharmacology study exploring the pharmacodynamic effect of two doses of TAR-0520 gel at 1.5% or 1% applied to two small skin areas (49 cm^2 each)

on the chest and the face. This is a Phase 1b study performed in healthy adult subjects.
Total study duration is approximately 8 weeks including a 4-week Screening phase and a 4-week Evaluation period.
In the first step of this study, TAR-520 gel will be applied daily (except week-ends) to 4 small 49 cm^2 skin areas for 3 weeks (15 applications). In a second step, after a short treatment-free period of 4 or 7 days (defined by a randomization list), a new single application of TAR-0520 will be conducted on the same test areas.
The first step will characterize the pharmacodynamics of TAR-0520, confirm the good local tolerance and identify a potential loss in vasoconstrictive potency over time. The second step will evaluate the effect of a treatment-free period on the vasoconstrictive response.

Screening period (approximately 30 subjects)

Step 1: Local tolerance and vasoconstrictive effect (skin blanching) on face and chest
Approximately 26 subjects randomized 2 concentrations of the test product (1.5% and 1%) and two product quantities applied (100 mg and 200 mg) will be tested in this study, for a total of 4 different treatment regimens:
- Regimen R1: 100 mg of TAR-0520 1.5% gel
- Regimen R2: 200 mg of TAR-0520 1.5% gel
- Regimen R3: 100 mg of TAR-0520 1% gel
- Regimen R4: 200 mg of TAR-0520 1% gel

Each participant will test 2 treatment regimens: one regimen will be tested on one side of the body (one cheek and the chest area) and another regimen will be tested on the other cheek and chest side.
Given that there are 4 different regimens and 2 body sides for each participant, each regimen will be tested in 13 participants.
Treatment regimen allocation will be determined by a randomization list

Test products applied to two areas: the cheek (7 cm x 7 cm) and a minizone of same surface area on the upper chest.
Once daily applications from Monday to Friday for 3 consecutive weeks, No application on Saturdays and Sundays

Local tolerance assessed visually at each visit on each test zone
Skin blanching evaluation on the 4 test zones by visual score on Day 1, 3 and 5 at T4H
Skin blanching evaluation by chromametry on Day 1, 3, 5, and 19 at T0H, T2H and T4H
Skin blanching evaluation by chromametry on Day 8, 12 and 15 at T0H and T4H
Step 2: Re-test following a treatment-free window
At the end of the third week of treatment, participants will enter a treatment-free period: half of the participants will have a 4-day treatment-free period and the other half a 7-day period. Duration of the treatment-free period will be defined randomly.

At the end of this treatment-free period, participants will have a last study visit where they will receive a last application of test product at the same regimen than received during the first treatment period.

Skin blanching evaluation by Chromametry at T0, T2H and T4H

Intervention Type
Drug

Phase

Phase I

Drug/device/biological/vaccine name(s)
TAR-0520 1.5% gel

Primary outcome(s)
Pharmacodynamic activity of TAR-0520 gel:
1. Skin blanching visual Score: Assessments will be done on the chest and the face minizones, 4 hours after products applications at Day 1, Day 3 and Day 5.
2. Chromametry: Chromametry assessments will be done on the chest and the face before products applications and 2 hours and 4 hours after products applications on Day 1, 3, 5, 19 and 23 or 26.
In addition, chromametry assessments will be done on the chest and the face before products applications and 4 hours after products applications on Day 8, D12 and D15.

Key secondary outcome(s)
1. Local tolerance of TAR-0520 when applied to the face assessed visually at each visit on each test zone
2. A safety assessment will be conducted for all subjects at the screening visit (from the Informed consent signature) and every subsequent visit. The safety parameters in this study include AEs, physical examination, vital signs assessments and a local tolerance evaluation on treated minizones.

Completion date
02/08/2024

Eligibility

Key inclusion criteria
1. Subject having signed an Informed Consent Form (ICF);
2. Male or female healthy subject with age ≥ 18 and < 60 years at the time of signing the ICF;
3. Subject having a phototype II to IV;
4. For female subject of childbearing potential: Non-pregnant (*) and non-lactating female who is abstinent or agrees to use effective contraceptive methods throughout the course of the study;
Acceptable birth control methods are the following:
- Intrauterine device in place for at least 1 month,
- Stable hormonal contraceptive for at least 1 month prior to dosing and continuing through study completion,
- Surgically sterilized partner,
- Male or female condom.
(*) Female subject must have a negative urine beta-human chorionic gonadotropin hormone (hCG) pregnancy test prior to dosing.
5. Normally active and in good health by medical history and physical examination;
6. Subject able to comprehend the full nature and the purpose of the investigation, including possible risks and side effects, and subjects able to cooperate with the Investigator and to comply with the requirements of the entire investigation (including ability to attend all the planned investigation visits according to the time limits), based on Investigator’s judgement.

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Upper age limit
59 Years

Sex
All

Total final enrolment
24

Key exclusion criteria
1. Female who is pregnant or breastfeeding or who plans to become pregnant during the study;
2. Clinically significant allergy (as judged by the investigator) or history of significant adverse reaction to brimonidine or related compounds, or to any of the excipients used (Drug product composition provided in the IB);
3. Current diagnosis of Raynaud's syndrome, thromboangiitis obliterans, orthostatic hypotension, severe cardiovascular disease, cerebral or coronary insufficiency, renal or hepatic impairment, scleroderma, Sjögren's syndrome, uncontrolled hypertension or diabetic microangiopathy;
4. Current treatment with brimonidine tartrate ophthalmic solution or gel;
5. Subject receiving monoamine oxidase (MAO) inhibitor therapy and subject on antidepressants which affect noradrenergic transmission (e.g., tricyclic antidepressants and mianserin);
6. Subject under a systemic treatment that might interfere with pharmacodynamic assessments such as beta-blockers, clonidine or calcium channel inhibitors (wash-out defined as 5 half-lives of the medication);
7. Subject with skin abnormalities (e.g. scars, excessive hair, tattooing) or any dermatosis (e.g. rosacea, seborrheic dermatitis, acne vulgaris) on the chest or the face;
8. Subject having been excessively exposed to ultraviolet radiation (UV), natural (sun) or artificial (tanning salon), in the 2 months before the initial visit or who plans such an exposure during the study;
9. Subject impossible to be contacted in case of emergency;
10. Subject currently participating or having participated in another clinical trial during the month preceding inclusion;
11. Subject who had been deprived of their freedom by administrative or legal decision or is under care of guardian or legal guardianship or subject hospitalized in a medical or social establishment for any reason.

Date of first enrolment
03/06/2024

Date of final enrolment
13/06/2024

Locations

Countries of recruitment
Mauritius

Study participating centre
CIDP
BioPark Mauritius, SOCOTA Phoenicia
Sayed Hossen Road,
Phoenix
Mauritius
73408

Sponsor information

Organisation
Tarian Pharma

Funder(s)

Funder type
Industry

Funder Name
Tarian Pharma

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