Sponsor:
Polfarmex S.A. Józefów 9 St., 99-300 Kutno, Poland Phone : +48 24 357 44 44
Investigational Medicinal Products (Study Drugs):
Test drug: Perindoprilum argininum + Indapamide SR, 10 mg + 1,5 mg, modified release tablets from Polfarmex S.A. **Reference drugs:** Reference 1 - Prestarium, 10 mg film-coated tablets from Les Laboratoires Servier Reference 2 - Tertensif SR 1,5 mg prolonged-release film-coated tablet from Les Laboratoires Servier
Clinical phase:
Bioequivalence study
Dose administered:
10 mg perindopril arginine 1,5 mg indapamide
Study title:
A Single-Dose, Bioequivalence Study of Perindopril arginine/Indapamide 10mg/1,5 mg Modified-Release Tablets versus Prestarium, 10 mg Film-Coated tablets Co-Administered with Tertensif SR 1,5 mg prolonged-release film-coated tablet in Healthy Volunteers under Fasting Conditions
Protocol No.
Protocol No. 01PERIN2025
Principal Investigator:
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Study Objectives:
The objectives of the study are as follows: • Preliminary: to analyse pharmacokinetic properties and bioequivalence of perindopril and indapamide from Perindoprilum argininum/Indapamide SR, 10 mg/1,5 mg, tablets from Polfarmex S.A. (Test product - T) and Prestarium, 10 mg film-coated tablets from Les Laboratoires Servier (Reference 1) and Tertensif SR 1,5 mg prolonged-release film-coated tablet Les Laboratoires Servier (Reference 2), • Secondary: to evaluate the safety and tolerability of these formulations.
Study design:
A single-center, open-label, single dose, randomized, two-sequence and two-period, crossover, bioequivalence study in fasted state with a wash-out period of at least 14 days (but not exceeding 21 days) between drug administrations in each treatment period. After eligibility screening, thirty-four (34) healthy male and female (aged ≥18 to ≤ 55 years) subjects will be randomized to receive a single dose of perindopril arginine and indapamide (10 mg + 1,5 mg) in two treatment periods, according to cross-over design. Subjects will receive treatment in the sequence: • TR – Period 1: test drug, Period 2: reference drug 1 and reference drug 2. • RT – Period 1: reference drug 1 and reference drug 2, Period 2: test drug. In each period, drug administration will be performed in a fasted state. Blood samples to determine plasma levels of perindopril and indapamide will be collected at regular intervals in each treatment period, up to 72 hours post-dose. Blood samples will be collected into tubes (around 10 ml) with anticoagulant K_2EDTA (or

other based on the bioanalytical method requirement) using cannula/direct venipuncture.
The volume of blood collected from one subject during each period will be around 350 ± 5 mL. The total volume of blood collected from one subject during the study will be around 700 ml ± 10 mL

The blood samples will be collected in the following time points:

For Perindopril

- Prior to administration of the medicinal product; point "0" or "pre-dose".
- 10, 20, 30, 40, 50 minutes and 1; 1.15 (1h 10 min), 1.5 (1h 30 min), 2; 2.5 (2 h 30 min); 3; 3.5 (3 h 30 min); 4; 4.5 (4h 30 min); 5; 6; 7; 8 hours after the medicinal product administration (19 samples)

For Indapamide:

- Prior to administration of the medicinal product; point "0".
- 1; 2; 3; 4; 6; 7; 8; 9; 10; 11; 12; 24; 36; 48 and 72 hours after the medicinal product administration (16 samples)

As a part of monitoring pharmacodynamic properties and safety, safety procedures will be conducted.

Screening (−21 to −2 days):
- Medical history; physical examination (including skin check for photosensitivity), vital signs with orthostatic measurements
- 12-lead ECG
- Clinical labs: haematology; biochemistry (ALT/AST/ALP/bilirubin, albumin/total protein, fasting glucose, creatinine/eGFR, urea, uric acid)
- Electrolytes (Na^+, K^+, Cl^-, Ca, Mg); urinalysis
- Serology: HBsAg, anti-HCV, HIV (per local law)
- Drugs of abuse (urine) and alcohol (breath) tests
- Pregnancy test (women).

Period admission (-1 day):
- Review of AEs/concomitant medications,
- Vital signs (with orthostatics)
- Alcohol/drug screen (per SOP),
- Pregnancy test (women),
- Final eligibility confirmation.

Pre-dose (0 day):
- Review of AEs/concomitant medications
- Vital signs (with orthostatics).

During study (2-4 h post dose and 8-12 h post dose):
- Review of AEs/concomitant medications
- Vital signs (with orthostatics).

Check-out:
- Review of AEs/concomitant medications
- Physical examination, vital signs with orthostatic measurements.
- 12-lead ECG[1]
- Clinical labs: haematology; biochemistry (ALT/AST/ALP/bilirubin, albumin/total protein, fasting glucose, creatinine/eGFR, urea, uric acid)[1]
- Electrolytes (Na^+, K^+, Cl^-, Ca, Mg); urinalysis[1]
- Serology: HBsAg, anti-HCV, HIV (per local law)[1]

- Pregnancy test (women[1]

Follow-up (7-12 days after completion of Period 2)

- Review of AEs/concomitant medications

[1] – *after the Period 2 only*

Study population:

Thirty-four (34) healthy male and female subjects fulfilling the inclusion criteria.

Inclusion criteria

1. Age ≥18 to ≤ 55 years old.
2. BMI ≥ 18.5 to ≤ 30.0 kg/m^2; body weight ≥50 kg (females) and ≥55 kg (males).
3. Ability to provide written informed consent and comply with study restrictions (including dietary limits and abstinence windows).
4. Non-smoker or nonuser of tobacco products for at least 1 month before the study (first administration).
5. Vital signs within normal limits: SBP 100–140 mmHg, DBP 60–90 mmHg, HR 50–90 bpm
6. Good general health as determined by medical history, physical examination, 12-lead ECG, and clinical laboratory tests (no clinically significant abnormalities).
7. Negative screening for drugs of abuse (urine) and alcohol (breath test).
8. Negative serology: HBsAg, anti-HCV, HIV (as per local regulations).
9. Women of childbearing potential: negative pregnancy test (screening and pre-dose) and agreement to use effective contraception. Men: agreement to use effective contraception per local standard.
10. No participation in other clinical studies and no blood/plasma donation within the washout specified by SOPs (e.g., 90 days).

Exclusion criteria

1. Major surgery within 3 months preceding the study (first administration), especially gastrointestinal surgeries that may affect drug absorption (e.g. bariatric procedures, gastric or intestinal resections).
2. Hypersensitivity to perindopril/other ACE inhibitors, indapamide/sulfonamide derivatives, or excipients (including lactose; congenital galactose intolerance, Lapp lactase deficiency, glucose-galactose malabsorption).
3. History of angioedema (hereditary, idiopathic, or ACEI-induced) or predisposition to angioedema.
4. Clinically significant electrolyte disorders: hypokalaemia (<3.5 mmol/L) or hyponatraemia; predisposition to ventricular arrhythmias.
5. Hyperkalaemia (>5.0 mmol/L) or concomitant use of potassium-sparing diuretics, potassium supplements, potassium-containing salt substitutes, or lithium.
6. Significant renal artery stenosis (bilateral or in a solitary kidney), clinically relevant renal or hepatic impairment; decompensated cardiovascular disease (e.g., symptomatic hypotension, unstable heart disease).
7. Clinically significant gastrointestinal disorders (including chronic hyperacidity, peptic ulcer disease, inflammatory bowel disease, malabsorption syndromes).
8. Pregnancy or breastfeeding.
9. Photosensitivity disorders/photodermatoses.
10. Any clinically significant systemic disease (cardiovascular, respiratory, gastrointestinal, endocrine, neurological, psychiatric) that may interfere with the study.
11. Abnormalities in the results of general medical examination and laboratory

testing that preclude subject's participation in the trial in the Investigator's opinion.
12. Abnormal ECG (e.g., QTcF ≥450 ms, significant conduction/arrhythmia findings) assessed by the Investigator as clinically relevant.
13. Positive results of HBsAg, anti-HCV or anti-HIV tests.
14. Positive tests for alcohol or drugs of abuse; inability/unwillingness to abstain from nicotine/caffeine/alcohol as required.
15. Acute infection/fever during screening; recent vaccinations per SOP (e.g., <14 days).
16. Use of prescription/OTC/herbal products within the washout period (typically ≥14 days; longer for enzyme inducers), especially those affecting the RAA system and electrolytes.
17. Participation in another clinical trial or blood/plasma donation within the washout period (e.g., 90 days).
18. Diet/lifestyle conflicting with protocol (food allergies, grapefruit/bergamot products, excessive caffeine, alcohol).
19. Any reason the subject is considered by the investigator to be an unsuitable candidate to participate in the study.

Primary PK parameters:

- $c_{max,}$ and AUC_{0-t} for perindopril
- $c_{max,}$ and AUC_{0-t} for indapamide

Secondary PK parameters

- T_{max}, $AUC_{0-\infty}$, AUC_%Extrap_obs, λ_z, $t_{1/2}$ for perindopril
- T_{max}, AUC_{0-72}, λ_z, $t_{1/2}$ for indapamide

Pharmacokinetics and statistical assessment:

The calculations of PK parameters will be derived using non-compartmental methods with Phoenix WinNonlin or other suitable.
Descriptive statistics will be computed and reported by treatment for the drugs concentrations in plasma at each sampling time point and for all primary and secondary PK parameters.
Ln-transformed values of primary PK parameters will be analysed using linear mixed effects model. The covariates in this model include sequence, period, formulation and subject nested in sequence as fixed effect. No random effects will be entered in the model.

Bioequivalence conclusion

The bioequivalence between the test and reference formulation will be concluded if:

- The 90% geometric confidence interval of the ratio (T/R) of least squares means of ln-transformed parameter ($AUC_{0-t,}$ C_{max}) is within bioequivalence acceptance interval of 80.00% - 125.00%.

Main Parameters of Safety

Medical history, clinical laboratory tests (haematology, blood biochemistry, urinalysis, serology), physical examination, vital signs (BP, HR), pregnancy test (females only), alcohol breath test, drugs of abuse tests, 12-lead ECG and adverse events.
Data is to be presented in individual listings and summary tables, and evaluated by descriptive statistics (mean, SD, median, range) where appropriate. All subjects who have taken 10 mg perindopril with 1.5 mg indapamide at least once in combination or separately are to be assessed.

Timelines

Inclusion of the first subject: 01.06 – 01.09.2026
Study A completed: 28.02.2027

Additional information

Clinical development program includes three Biostudies – single dose under fasting conditions, single dose after fed conditions and after multiple dosing.