CLINICAL STUDY PROTOCOL
No. PBTZ169-Z00-C01-1

Open-label, prospective, single-arm study of PBTZ169 safety, tolerance and pharmacokinetics study in healthy volunteers after single and multiple oral administrations with dose escalation

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1 STUDY SUMMARY

Study title	Open-label, prospective, single-arm study of PBTZ169 safety, tolerance and pharmacokinetics study in healthy volunteers after single and multiple oral administrations with dose escalation
Study ID/code	PBTZ169-Z00-C01-1
Study phase	phase I, first in human
Planned study period	01.12.2015 – 01.09.2016
Study objectives	To investigate safety and tolerance and evaluate the pharmacokinetics of PBTZ169, capsules 40 mg, in healthy volunteers after single administration under fasting condition at rising doses (40 mg, 80 mg, 160 mg, 320 mg, 640 mg) and multiple administration under fasting conditions at doses that will be defined according to the results of the analysis of the drug's tolerance, safety and pharmacokinetics after single administration.
Study tasks	• To evaluate safety and tolerance of PBTZ169, capsules 40 mg, in healthy volunteers after single administration under fasting condition at rising doses (40 mg, 80 mg, 160 mg, 320 mg, 640 mg) and multiple administration under fasting conditions at doses that will be defined according to the results of the analysis of the drug's tolerance, safety and pharmacokinetics after single administration, on the basis of recording all possible adverse events. • To evaluate effects of PBTZ169, capsules 40 mg, on vital functions (blood pressure, HR, body temperature, RR) in healthy volunteers after single administration under fasting condition at rising doses (40 mg, 80 mg, 160 mg, 320 mg, 640 mg) and multiple administration under fasting conditions at doses that will be defined according to the results of the analysis of the drug's tolerance, safety and pharmacokinetics after single administration. • To evaluate effects of PBTZ169, capsules 40 mg, on investigations (complete blood count, blood biochemistry, coagulogram, urinalysis, ECG) in healthy volunteers after single administration under fasting condition at rising doses (40 mg, 80 mg, 160 mg, 320 mg, 640 mg) and multiple administration under fasting conditions at doses that will be defined according to the results of the analysis of the drug's tolerance, safety and pharmacokinetics after single administration. • To evaluate pharmacokinetic parameters of PBTZ169, capsules 40 mg in healthy volunteers after single administration under fasting condition at rising doses (40 mg, 80 mg, 160 mg, 320 mg, 640 mg): maximum concentration Cmax, time to maximum concentration Tmax, areas under the curve AUC0-t and AUC0-∞, ratio of AUC0-t to AUC0-∞, half-life T1/2, mean retention time MRT, total clearance Clt, distribution volume Vd, elimination constant kel.

	• To evaluate pharmacokinetic parameters of PBTZ169, capsules 40 mg, after multiple administration under fasting conditions at doses that will be defined according to the results of the analysis of the drug's tolerance, safety and pharmacokinetics after single administration in healthy volunteers, i.e.: maximum concentrations C_{max} and $C_{max,ss}$, trough concentration after multiple administration C_{trough}, time to maximum concentration T_{max} and $T_{max,ss}$, areas under the curve AUC_{0-t}, $AUC_{0-\infty}$ and AUC_{ss}, half-life $T_{1/2}$, mean retention time MRT, total clearance Cl_t, distribution volume V_d and V_{ss}, elimination constant k_{el}. □ To evaluate the elimination kinetics of PBTZ169, capsules 40 mg, in urine (renal clearance Cl_{ren}) in healthy volunteers after single administration under fasting condition at rising doses (40 mg, 80 mg, 160 mg, 320 mg, 640 mg) and multiple administration under fasting conditions at doses that will be defined according to the results of the analysis of the drug's tolerance, safety and pharmacokinetics after single administration.
Planned number of the study centers and their location	At the territory of the RF, the participation of 3 study centers is planned
Design and methodology	It is open-label safety, tolerance and pharmacokinetics study with intra-cohortal randomization of PBTZ169, capsules 40 mg in healthy volunteers after single and multiple oral administrations. The study includes two stages: • - ***Stage 1*** - single dosing with dose escalation • - ***Stage 2*** - multiple dosing with dose escalation. ***Stage 1 (single dosing with dose escalation)*** Totally, 5 cohorts (C1-C5) are planned to be enrolled during the first stage of the study with 7 subjects in each (6 volunteers and 1 back-up) to investigate the drug after single administration. Screening procedures to include volunteers into each cohort will be performed within 7 days before the drug prescription. Healthy volunteers complying with the study inclusion criteria, will be admitted to hospital in the evening before the test drug administration and randomized into the main group and back-up group. Healthy volunteers complying with the study inclusion criteria will be included successively into the following cohorts: • Cohort 1 (C1) includes 6 healthy volunteers of the main group each of whom received a single dose of the drug - 1 capsule containing 40 mg of PBTZ169 and 1 healthy back-up volunteer. • Cohort 2 (C2) includes 6 healthy volunteers of the main group each of whom received a single 80 mg dose of PBTZ169 (2 capsules 40 mg) and 1 healthy back-up volunteer.

	• Cohort 3 (C3) includes 6 healthy volunteers of the main group each of whom received a single 160 mg dose of PBTZ169 (4 capsules 40 mg) and 1 healthy back-up volunteer. • Cohort 4 (C4) includes 6 healthy volunteers of the main group each of whom received a single 320 mg dose of PBTZ169 (8 capsules 40 mg) and 1 healthy back-up volunteer. • Cohort 5 (C5) includes 6 healthy volunteers of the main group each of whom received a single 640 mg dose of PBTZ169 (16 capsules 40 mg) and 1 healthy back-up volunteer. In Cohort 1, initially 3 volunteers from the main group will receive the drug simultaneously and the rest 3 volunteers will receive the drug 24 h after it will be have been taken by previous volunteers. In the successive Cohorts, all 6 volunteers of the main group will receive the drug simultaneously. Before the volunteers will be included into Cohort 2, the drug pharmacokinetic results will have been received for Cohort 1. Time points for blood and urine sampling can be adjusted for all successive cohorts based on the data concerning pharmacokinetics and safety of administration of PBTZ169 capsules 40 mg. Screening of volunteers into each successive cohort can be started not earlier than 24 h after all the volunteers from the previous cohort have received the drug. The subjects will be randomized within the cohort after volunteers from previous cohort have received the drug. The volunteers of each successive cohort will administer single dose of the drug minimum 7 days after the volunteers from the previous cohort have received the drug if dose-limited toxicity (DLT) is found in less than 50% volunteers from the group. For Cohort 1, DLT reported in 2 volunteers from the first three patients will be considered as achievement of this criterion and will result in the study termination, thus, the successive three subjects will not be included into the study. In this study, DLT will include any class 3 and more toxicity according to Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials which is "possibly", "probably" and "definitely" related with the administration of PBTZ169. The volunteers from each group will be admitted to hospital in the evening before dosing. Back-ups from cohorts C1-C5 will be admitted to hospital simultaneously with the main volunteers of the cohorts for not more than 24 h and will be discharged and complete the study participation

	if their participation is not necessary. If back-up is necessary in any cohort, the period of hospitalization and all the study procedures for respective back-up will be equivalent to those for substituted volunteer. In Cohort 1, back-up will be hospitalized with the second three volunteers. Each healthy volunteer from the main groups of cohorts C1-C5 will receive only one dose of the test drug in the morning under fasting conditions (10 h of night fasting) with 300 mL of bottled water. On the day of administration, water intake is ad libitum, except for 1 h within the drug administration during which water intake is prohibited and for 4 h after the drug administration (water intake is prohibited during the first hour, water intake will be limited by 100 mL of bottled water ever hour for the successive 3 h). Food intake will be prohibited for 4 h after the drug administration. Volunteers from cohorts C1 and C2 will have their venous blood samples taken to determine PBTZ169 concentration before the drug administration: -5 min, 0 min, afterwards at the following time points after the drug administration: in 0:10, 0:20, 0:30, 0:45, 1:00, 1:30, 2:00, 2:30, 3:00, 3:30, 4:00, 5:00, 6:00, 8:00, 10:00, 12:00 and 24:00 (h:min). Volunteers from Cohort 3 will have their venous blood samples taken to determine PBTZ169 concentration before the drug administration: -5 min, 0 min, afterwards at the following time points after the drug administration: in 0:10, 0:20, 0:30, 0:45, 1:00, 1:30, 2:00, 2:30, 3:00, 3:30, 4:00, 5:00, 6:00, 8:00, 10:00, 12:00, 48:00 (h:min). Volunteers from Cohort 4 will have their venous blood samples taken to determine PBTZ169 concentration before the drug administration: -5 min, 0 min, afterwards at the following time points after the drug administration: in 0:10, 0:20, 0:30, 0:45, 1:00, 1:30, 2:00, 3:00, 4:00, 5:00, 6:00, 8:00, 10:00, 12:00, 24:00 and 48:00 (h:min). Volunteers from Cohort 5 will have their venous blood samples taken to determine PBTZ169 concentration before the drug administration: -5 min, 0 min, afterwards at the following time points after the drug administration: in 0:10, 0:20, 0:30, 0:45, 1:00, 1:30, 2:00, 3:00, 4:00, 5:00, 6:00, 8:00, 10:00, 12:00, 24:00, 48:00 and 72:00 (h:min). At every time point of blood sampling for PBTZ169 concentration determination, additional venous blood will be also sampled for further storage of samples for possible determination of additional parameters. Additional blood can be sampled to control the current parameters to assure safety of volunteers. Urine will be sampled from every volunteer in each of cohorts during the first 24 hours after dosing within the the following time

periods: 0–2, 2–6, 6–12 and 12–24 h to evaluate pharmacokinetics. 12-24 h urine samples will be analyzed only at non-zero concentration of PBTZ169 in 6-12 h sample.

During the whole period of blood sampling for pharmacokinetics after the drug administration, the volunteers will be at hospital and will be discharged after all procedures planned in the protocol have been finished, afterwards the monitoring will be continued under out-patient conditions.

Thus, total in-patient period for every cohort will be as follows:

- C1 and C2 - 3 days (including the admission day, day of the test drug administration and 24 h after the drug administration)
- C3 and C4 - 4 days (including the admission day, day of the test drug administration and 48 h after the drug administration)
- C5 - 5 days (including the admission day, day of the test drug administration and 72 h after the test drug administration).

After the discharge from hospital, volunteers from C1-C5 should visit the study center in 5±1 days after the drug administration for follow-up procedures (safety evaluation).

14±1 days after the drug administration, the last visit (Visit 3) will take place in the form of phone contact after which the volunteers will finish the study participation. Thus, total follow-up period will be 14 days after the drug administration for each volunteer.

After the last volunteer from those enrolled in the cohorts of Stage 1 completes the study, safety and pharmacokinetics will be analyzed using the data of all cohorts of a single dose study. Upon the termination of an analysis of the data obtained during the Stage I, an independent Committee for data evaluation and study subjects' safety will be called. The results of the session of the Committee dedicated to the discussion of the data obtained in the first 5 cohorts (the results of the statistical analysis) will serve for preparing a resolution about the safety, tolerance and pharmacokinetics of the drug taken once in the first 5 cohorts. Takin into account the resolution of the independent Committee about the data evaluation and the safety of study subjects, the Sponsor will:

- ***Determine the doses of PBTZ-169 for multiple administration during the Stage 2 of the study;***
- ***Take the decision on the necessity to adjust blood and urine sampling timepoints ;***
- ***Take the decision about the necessity of a study procedure correction.***

According to the results of the analysis of all the data obtained after the completion of the study by all volunteers from cohorts 1 to 5, a clinical study report will be prepared.

Stage 2 (multiple dosing with dose escalation)

Up to 3 cohorts are planned to be enrolled during the second stage of the study with 6 subjects in each to investigate the drug after multiple administration.

Volunteers complying with the study inclusion criteria will be included successively into the following cohorts for multiple drug administration:

- Cohort 6 (C6) includes 6 healthy volunteers each of whom will receive X* mg of PBTZ169 daily under fasting conditions once a day in the morning at the same time ±15 min for 14 days.
- Cohort 7 (C7) includes 6 healthy volunteers each of whom will receive Y* mg of PBTZ169 daily under fasting conditions once a day in the morning at the same time ±15 min for 14 days.

∗The dose of PBTZ-169 will be defined taking into account the results of the data analysis and the conclusions of the independent Committee for data evaluation and study subjects‘ safety.

The same inclusion criteria will be used to select volunteers into cohorts C6-C7 as those used to select volunteers into Cohorts 1-5.

If two or more volunteers drop out from multiple administration cohorts before the study Day 7 inclusive due to different reasons, except for AE/SAE, according to Sponsor's decision, volunteers can be additionally enrolled by the number of drop outs for whom an additional screening will be performed. Up to 4 back up volunteers are supposed to be additionally required for each of multiple dosing cohorts. If back-up is necessary in multiple dosing cohort, the period of hospitalization and all the study procedures for a back up will be equivalent to those for substituted volunteer.

Screening procedures to include volunteers into each cohort will be performed within 10 days before the drug prescription.

Screening of volunteers into Cohort 7 can be started not earlier than 24 h after all the volunteers from the previous cohort have received the last dose of the drug.

The drug administration in Cohort 7 can be started not earlier than 7 days after all the volunteers from the previous cohort administer the last drug dose if DLT is reported in less than 50% volunteers from the previous cohort before the latest volunteer is discharged from the hospital. DLT will include any class 3 and more toxicity according to Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials which is "possibly", "probably" and "definitely" related with the

	administration of PBTZ169. Volunteers included in cohorts C6-C7 are hospitalized in the evening on Day 0 before the first drug dose administration. In the evening of Day 1, every healthy volunteer will take the first dose of the test drug under fasting condition (10 h of night fasting) with 300 mL of bottled water. Afterwards the volunteers will continue daily administration of the test drug at constant dose (depending on the cohort) under in-patient conditions. The drug will be administered daily under fasting condition (10 h of night fasting) o.d. in the morning at the same time ±15 and always with 300 mL of bottled water. Food intake is prohibited for the volunteers during 4 hours after the first, 7th and last (14th) dose of the test drug; water intake will be also regulated during this time: not more than 100 mL of bottled water per hour. On the days of the rest drug administrations, the volunteers are prohibited to take food for 2 h after the drug administration; water intake will be also regulated during this time: not more than 100 mL of bottled water per hour. The drug administration period will be 14 days. Before and after the administration of the first, 7th and last (14th) dose of the test drug, venous blood will be taken from the volunteers to determine PBTZ169 concentration at the following time points: before the first drug dose administration: 0 min (before the drug administration) and for 24 h after the administration of the first, 7th and last (14th) dose of the test drug in: 0:15, 0:30, 0:45, 1:00, 1:30, 2:00, 3:00, 4:00, 6:00, 8:00, 10:00, 12:00, 24:00 (h:min after the drug dosing). 24 h point after the administration of 1 and 7 drug doses should be taken before the successive doses. During drug administration days 3-6 and 9-13, venous blood will be daily taken at 0 min time point (before the drug administration) to determine PBTZ169 concentration. Blood will be sampled at 48 h and 72 h time points after the administration of the last (14) drug dose. The deviations from the specified time by 10 min to one or another side (± 10 min) are acceptable for the following time points: 24 hours for administration of the first, 7th and last (14th) doses of the test drug. For 48 h and 72 h time points after the last (14th) dose administration, deviation from the specified time by 20 min to one or another side (± 20 min) is acceptable. For the rest time points, blood sampling after the test drug administration can deviate by not more than 2 min to one or another side (± 20 min). In case of preterm withdrawal from the study, if there is no risk for a volunteers, attempts to sample their blood according to schedule for the last (14) dose will be taken. At every time point of blood sampling for PBTZ169

	concentration determination, additional venous blood will be also sampled for further storage of samples for possible determination of additional parameters. Urine will be sampled from every volunteer in each of cohorts during the first 24 hours after the first and last dosing within the the following time periods: 0–2, 2–6, 6–12 and 12–24 h to evaluate pharmacokinetics. 12-24 h urine samples will be analyzed only at non-zero concentration of PBTZ169 in 6-12 h sample. During the whole period of PBTZ169 administration, the volunteers will be monitored in the hospital; afterwards the monitoring will be continued under outpatient conditions. Total follow-up period will be 14 days after the last drug dose administration for each volunteer. After the discharge from the hospital, volunteers from cohorts C6-C7 should visit the study center in 1 and 2 days for blood sampling at 48 h and 72 h time points and in 7±1 days and 14±1 days for the last drug dosing (the study Day 19±1 and Day 28±1) for follow up procedures (safety evaluation). 21±1 days after the last drug dosing (the study Day 35±1) in volunteers from cohorts C6-C7, final visit will be performed in the form of phone contact after which the volunteers will finish the study participation. For patients, who will receive multiple dosing, hospitalization period will be 16 days (including admission day, 14 days of the test drug administration and 24 h of patient monitoring under inpatient conditions after last drug dosing). The results obtained in this study will be used to plan subsequent safety and efficacy clinical studies of PBTZ169.
Justification of dose selection	***Dose selection for single dosing*** Maximum recommended initial dose (MRID) will be calculated on the basis of recommendations of Methodological Recommendations for determination of safe dose of drug for phase I clinical studies in adult volunteers (Guidelines for nonclinical studies of drugs, part one, 2012). ***Determination of no observed adverse effect level (NOAED)*** Nonclinical investigation of subchronic toxicity of finished dosage form was performed in rats after intragastric administration of the drug at API doses of 9-180 mg/kg/daily for 30 days and on rabbits at API doses of 8–32 mg/kg/daily for 30 days. The results of studies demonstrated that NOAED in rats was 180 mg/kg and that in rabbits was 32 mg/kg. While investigating subchronic toxicity of the drug in rabbits, death of one male, which received API dose of 8 mg/kg, was reported on the drug administration day 9. However, this case was treated as accidental death not associated with the drug

	administered. Nonclinical investigation of acute toxicity of finished dosage form was performed in rats after intragastric administration of the drug at API doses of 9-360 mg/kg and on rabbits at API doses of 8–32 mg/kg. No fatal cases, gender distinctions and differences from the control groups were reported. ***Calculation of human equivalent dose (HED) based on NOAED*** Calculation factor 6 was used for calculation of HED in rats and calculation factor 3.2 was used for that in rabbits. HED calculated based on NOAED in rats for 30 mg/kg [180 (mg/kg)/6]. HED calculated based on NOAED in rabbits for 10 mg/kg [32 (mg/kg)/3.2]. ***Selection of the most suitable animal species for HED determination*** In toxicity evaluation experiments in rats and rabbits, the test drug had no effect on the appearance, general condition, physiological parameters, did not affect negatively hematological and biochemical blood parameters and vital signs; did not cause pathomorphological changes. Thus, taking into consideration that use of the lowest HED assures the safest initial human dose, the most suitable species is rabbits (calculated HED is 10 mg/h). ***Use of safety coefficient, determination of MRID*** Standard safety coefficient 10 is used in the calculation of MRID. MRID is 1 mg/kg [10 (mg/kg)/10]. ***Determination of pharmacologically active dose (PAD)*** Anti-tuberculosis activity of the drug substance was determined on experimental model of acute and chronic tuberculosis in mice and in experimental chronic tuberculosis in guinea pigs. In the experiments, PAD in mice was 25 mg/kg. HED calculated using PAD in mice was 2.08 mg/kg [25 (mg/kg)/12.0]. In the experiments, PAD in guinea pigs was 80 mg/kg. HED calculated using PAD in guinea pigs was 17.02 mg/kg [80 (mg/kg)/4.7]. Thus, HED calculated on the basis of substance activity study varies between 2.08 and 17.02 mg/kg. Taking into consideration that HED calculated using PAD value higher than MRID, initial dose (dose for Cohort 1) will be 1 mg/kg (for subject with 70 kg of body weight complies with 70 mg dose). As volunteers with body weight less than 70 kg can

	participate in the study, taking into consideration that PBTZ169 is a novel drug and that the test drug has been manufactured at dose of 40 mg, 40 mg dose will be administered as an initial dose. Maximum dose for this study will be 640 mg as a single dose. Maximum dose can be selected on the basis of lack of negative drug effects when administered at API doses up to 180 mg/kg (HED=30 mg/kg, calculated for a human of 70 kg in body weight - 2100 mg) in rats in subchronic toxicity study, up to 360 mg/kg (HED=60 mg/kg, calculated for a human of 70 kg in body weight - 4200 mg) in rats in acute toxicity study. Thus, selected maximum dose 640 mg is within the range of investigated doses in animals (rats) up to 2100-4200 mg. ***Dose selection and period of administration for multiple dosing*** Doses of PBTZ169 for multiple administration will be defined taking into account the results of the data analysis upon study completion by the volunteers from Cohorts 1 to 5, and the conclusions of the independent Committee for data evaluation and study subjects' safety. Two different doses are expected to be chosen for multiple dosing. Good tolerance and safety of the corresponding single dose of the drug will be the defining criteria, including also a determination of a dose-limiting toxicity (DLT) in less than 50% of the volunteers from the respective cohort with single dosing. Presumably, two highest doses among those studied in single administration will be selected, on the condition of a good tolerance of the drug. Multiple administration of PBTZ169 will be performed at hospital under thorough monitoring of volunteers. Taking into consideration that the drug administration period in rabbits and rats was 30 days in the subchronic toxicity study and 180 days in the chronic toxicity study, according to Guidelines for drug evaluation, 2013 (volume I), 14-day period of the test drug administration in this clinical study is justified.
Planned number of study subjects	At ***Stage 1****,* 53 volunteers are planned to be screened (taking into consideration supposed withdrawal of 18 subjects - 50% of planned number of subjects included at screening stage) which will result in inclusion of totally 35 healthy volunteers complying with inclusion criteria: 6 male volunteers of the main group into each of 5 cohorts of single dosing and one back-up in each cohort at the first stage. At ***Stage 2****,* 30 volunteers are planned to be screened (taking into consideration supposed withdrawal of 15 subjects - 50% of planned maximum number of subjects included at screening stage) which will result in inclusion of totally up to 20 healthy volunteers complying with inclusion criteria: 6 male volunteers of the main group into each of 2 cohorts of multiple dosing (C6 and C7) with possible additional inclusion of 4 volunteers into each cohort in case of withdrawal at the second stage.

	Total number of screened volunteers during the both study stages will be up to 83 subjects. Total number of volunteers included at the both study stages will be up to 55 subjects. As the main tasks of this study are safety and tolerance evaluation and the study is not comparative in design, acceptable from this point of view sample size for such clinical studies has been chosen which allows, first of all, to study safety and tolerance profile of the test drug.
Selection criteria	At each of two stages, healthy male volunteers aged 18 to 45 years old are planned to be included into the study according to inclusion criteria with no non-inclusion criteria. Similar selection criteria are used for all cohorts.
Inclusion criteria	Volunteers complying with each of the following criteria will be included into the clinical study: 1. Written informed consent received from a volunteer. 2. Men aged 18 to 45 years old, inclusive. 3. Body mass index of 18.5–25 kg/m^2. 4. Verified diagnosis: "healthy" according to data of standard clinical, laboratory and instrumental examination methods performed at screening: • Absence of deviations of physical examination parameters and vital signs (systolic blood pressure - 100-129 mm Hg, inclusive; diastolic blood pressure - 70-89 mm Hg, inclusive; heart rate - 60-80 bpm, inclusive); • Absence of deviations of laboratory parameters (complete blood count, blood biochemistry, HIV, HBV, HCV, syphilis and urinalysis); • Normal parameters of 12-lead ECG; • Normal results of photofluorographic or X-ray examination (the results received maximum 6 months before screening can be used); • Normal blood glucose levels during the oral glucose tolerance test (less than 5.6 mmol/l at fasting state and less than 7.8 mmol/l 2 hours after glucose charge). This test is only used for volunteer inclusion screening in cohorts with multiple dosing. 5. Ability, according to investigator, to comply with all requirements of the protocol. 6. Agreement to use double contraception method during the study participation and for 3 months after the test drug administration - combination of male condom with not less than one of the following methods: • female partner using hormonal contraception; • using aerosols, creams, suppositories and other agents containing spermicides; • female partner using intrauterine device.
Non-inclusion criteria	Volunteers who will comply with at least one of the following criteria will not be included in the clinical study:

	1. Aggravated allergic history, including presence of at least one episode of drug allergy. 2. Chronic diseases of cardiovascular, bronchopulmonary, neuroendocrine systems, ENT and gastrointestinal, hepatic, renal, blood and cutaneous diseases. 3. Chronic diseases of eyes except for myopia, hypermetropia and mild to moderate astigmatism. 4. Gastrointestinal surgeries (except for appendectomy performed not more than 1 year before screening). 5. Acute infections within less than 4 weeks before screening. 6. Regular drug administration within less than 4 weeks before screening. 7. Regular administration or application (including topical) of hormonal drugs for more than 1 week within less than 45 days before the screening. 8. Administration of drugs exerting evident effects on hemodynamics, hepatic function, etc. (barbiturates, omeprazole, cimetidine, etc.) within less than 45 days before the screening. 9. Positive test for narcotic and psychotropic agents. 10. Donation (450 mL of blood or plasma) within less than 3 months before the screening. 11. Intake of more than 10 U of alcohol per week (1 unit of alcohol is equivalent to 500 mL of beer, 200 mL of vine or 50 mL of strong alcoholic drink) or historical data on alcoholism, narcomania, drug abuse. 12. Mental illnesses. 13. Smoking within half a year before the screening. 14. Previous participation in this clinical study and withdrawal from it due to any reason. 15. Participation in other clinical studies of drugs within less than 6 months before the screening. 16. Planned conception or sperm donation during the study after the test drug administration or during 3 months after the date of the last drug administration.
Withdrawal criteria	Withdrawal criteria should be considered as follows: 1. Volunteer's refusal to participate in the study at any stage of its performance. 2. Occurrence of adverse event, including serious adverse event: individual intolerance of the test drug, hypersensitivity to the drug ingredients found directly in the drugs administration due to which further participation in the study is not possible. 3. Intolerance of the study procedures by a volunteer. 4. Any event or volunteer's condition which, according to investigator, makes further participation of the volunteer in

	the study impossible. 5. Misbehavior of a volunteer (including if the volunteer was admitted to hospital later than appointed), loss of contact with a volunteer (including due to change of residence). 6. Intake of alcohol or products containing grapefruit, pomelo, cranberry and their juices is prohibited 72 h before the drug administration and further till the end of participation in the study. 7. Vomiting during the first 4 hours after the drug administration. 8. Inclusion of volunteer into the study in case of incompliance with the inclusion/non-inclusion criteria. 9. Study termination by the Sponsor. 10. Study termination by the Investigator. 11. Study termination by the Regulatory Authorities. If patient is withdrawn from the study due to any reason, all biosamples collected will be analyzed and investigators will make attempts to obtain maximum complete information on volunteer (including collection of biosamples and clinical information unless informed consent is withdrawn) to assure his safety. If a volunteer is withdrawn from the study cohorts C1-C7 before dosing and during 4 months since dosing (for volunteers of C1-C5) or before the end of visit on the drug administration day 7 (for volunteers of C6-C7) due to the following reasons, a withdrawn patient can be substituted with a back-up according to the Investigator: 1. Refusal of a volunteer to participate in the study. 2. Intolerance of study procedures by a volunteer. 3. Any event or volunteer's condition which, according to investigator, makes further participation of the volunteer in the study impossible. 4. Misbehavior of a volunteer (including if the volunteer was admitted to hospital later than appointed), loss of contact with a volunteer (including due to change of residence). 5. Intake of alcohol or products containing grapefruit, pomelo, cranberry and their juices is prohibited 72 h before the drug administration and further till the end of participation in the study. 6. Inclusion of volunteer into the study in case of incompliance with the inclusion/non-inclusion criteria. Substitution of 1 volunteer is possible in each of cohorts C1-C5. In each of cohorts C6-C7, a volunteer can be substituted only if two or more volunteers are withdrawn while the substitution will not be performed if 1 volunteer is withdrawn.

Test drug	PBTZ169 capsules for oral administration, 40 mg
Dose and administration route	***Single oral:*** • Cohort 1 — 40 mg • Cohort 2 — 80 mg • Cohort 3 — 160 mg • Cohort 4 — 320 mg • Cohort 5 — 640 mg ***Multiple oral*** • Cohort 6 — X* mg/day • Cohort 7 — Y* mg/day ∗The dose of PBTZ-169 will be defined taking into account the results of the data analysis and the conclusions of the independent Committee for data evaluation and study subjects‘ safety.
Administration period	Single administration in the morning at a fasting state for volunteers from cohorts C1-C5. For volunteers from cohorts C6-C7: daily drug administration o.d. in the morning at a fasting state at the same time±15 min for 14 days.
Reference drug	Not applicable.
Respective therapy	Not applicable.
Primary and secondary variables	***Safety and tolerance variables evaluated*** • Adverse events • Changes in vital signs • Results of laboratory analyses (complete blood count, blood biochemistry, urinalysis) • Results of ECG • Results of physical examination ***Pharmacokinetic parameters evaluated (single dosing)*** • Maximum concentration (C_{max}) • Time to maximum concentration (T_{max}) • Area under the concentration-time curve from 0 to last blood sampling (t) (AUC_{0-t}) • Area under the concentration-time curve from zero to infinity ($AUC_{0-\infty}$) • Ratio AUC_{0-t} to $AUC_{0-\infty}$ ($AUC_{0-t}/AUC_{0-\infty}$) • Total clearance (Cl) • Renal clearance (Cl_{ren}) • Distribution volume (V_d) • Half-life ($T_{1/2}$) • Mean retention time (MRT) • Absorption rate (C_{max}/AUC_{0-t})

	Pharmacokinetic parameters evaluated (multiple dosing) • Maximum concentration (C_{max}) • Maximum steady-state concentration ($C_{max,ss}$) • Trough concentration after multiple administration (C_{trough}) • Time to maximum concentration (T_{max}) • Time to maximum steady-state concentration ($T_{max,ss}$) • Area under the concentration-time curve from 0 to last blood sampling (t) (AUC_{0-t}) • Area under the concentration-time curve from zero to infinity ($AUC_{0-\infty}$) • Steady-state area under the concentration-time curve (AUC_{ss}) • Total clearance (Cl_t) • Renal clearance (Clren) • Apparent distribution volume (V_d) • Steady-state distribution volume (V_{ss}) • Half-life ($T_{1/2}$) • Mean retention time (MRT) • Elimination constant k_{el}
Statistical methods	The study results will be statistically analyzed in the following populations: • Intent-to-treat population - comprises of all the participants who underwent screening and comply with all the selection criteria. The population will be used for listings and presentation of data by participants' disposition. • Safety population - consists of participants who administered the test drug (for Cohorts C6-C7 - at least once). It will be used for analysis and evaluation of demographic and other baseline data and all safety parameters including adverse events, physical examination, evaluation of vital signs, previous and current therapy, ECG and all the rest instrumental examination methods, all laboratory investigations. • Population for single dosing pharmacokinetics evaluation consists of all participants who administered the test drug and have at least 1 measure of the test drug concentration. Calculation of PK parameters and their statistical processing will be performed on this population. • Population for multiple dosing pharmacokinetics evaluation consists of all participants who administered the test drug at least 7 times and have measure of the test drug concentration after the first and seventh administration of the test drug. For multiple dosing cohorts, calculation of PK parameters and their statistical

	processing will be performed on this population. ***Safety parameters evaluation*** Safety evaluation will include determination of AE/SAE, vital signs, ECG data, physical examination and laboratory analyses in the safety population. All the safety parameters will be performed using descriptive statistics parameters (mean, standard deviation, median, minimum and maximum, range, quartiles, number of valid cases - for quantitative variables; absolute count, ratio, distribution - for qualitative variables). ***Pharmacokinetic parameters*** Pharmacokinetic parameters will be determined using WinNonlin software (Phoenix Inc) by the results of the drug concentration measurement. Individual pharmacokinetic curves will be plotted with determination of all calculable parameters and descriptive statistics parameters.