CLINICAL STUDY PROTOCOL
№ PBTZ169-Z00-C01-3

Open-label prospective study to evaluate the safety, tolerability, pharmacokinetics and the effect of food of medicinal product PBTZ169 in 80 mg capsules when used in increasing doses in healthy volunteers

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1 STUDY SUMMARY

Study name	Open prospective study to evaluate the safety, tolerability, pharmacokinetics and the effect of food of medicinal product PBTZ169 in 80 mg capsules when used in increasing doses in healthy volunteers
Identification number/study code	PBTZ169-Z00-C01-3
Study phase	Phase I
Planned study dates	Expected duration of the study – 7 months. Recruitment period is approximately 10 days. Maximum duration of participation of one volunteer in the study at the first stage (dose escalation when used once or twice, effect of food when used once) – 24 days, at the second stage (repeated use) – 30 days.
Study goals	At the first stage – study the safety, tolerability and evaluate the pharmacokinetics of PBTZ169, 80 mg capsules, in healthy volunteers when administered once or twice on an empty stomach successively in increasing doses (640, 960, 1280 mg once a day and 640 mg twice daily), evaluate the effect of food with single administration of the product at a dose of 640 mg. At the second stage – study the safety, tolerability and evaluate the pharmacokinetics of PBTZ169, 80 mg capsules, in healthy volunteers with repeated use for 14 days, at a dose and following a regimen (on an empty stomach or after meal, once a day or twice day) determined by results of analysis of tolerability, safety and pharmacokinetics after the completion of the first stage of the study.
Study objective	***Main objectives*** • Evaluate the safety and tolerability of PBTZ169, 80 mg capsules, in healthy volunteers once or twice on an empty stomach in increasing doses (640, 960, 1280 mg once daily and 640 mg twice daily) and repeated administration for 14 days at maximum dose and following a regimen determined by results of analysis of tolerability, safety and pharmacokinetics after the completion of the first stage of the study. • Evaluate the effect of food on the pharmacokinetics of PBTZ169, 80 mg oral capsules at a dose of 640 mg. Compare the test (T) method of administration (8 80 mg capsules after meal) with the reference (R) method of administration (8 80 mg capsules on an empty stomach). ***Secondary objectives*** • Evaluate the safety of PBTZ169 based on all possible adverse events.

	• Evaluate the effect of PBTZ169 on vital signs (blood pressure, HR, body temperature, RR) and results of physical examination. • Evaluate the effect of PBTZ169 on laboratory and instrumental examinations (complete blood count, biochemical blood test, urine analysis, ECG). • To evaluate the pharmacokinetic parameters of PBTZ169, 80 mg capsules, in healthy volunteers when used once or twice on an empty stomach in increasing doses (640, 960, 1280 mg once a day and 640 mg twice daily): maximum concentration C_{max}, time to reach maximum concentration T_{max}, area under the pharmacokinetic curve AUC_{0-t} and $AUC_{0-\infty}$, half-life $T_{1/2}$, total clearance Cl_t/F, volume of distribution V_d/F, elimination constant k_{el}. • Evaluate the pharmacokinetic parameters of PBTZ169, 80 mg capsules, with repeated use for 14 days at the maximum dose and following a regimen determined by results of analysis of tolerability, safety and pharmacokinetics after the completion of the first stage of the study in healthy volunteers, namely: maximum concentration of C_{max}, residual concentration with repeated use of C_{trough}, time to reach the maximum concentration T_{max}, area under the pharmacokinetic curve AUC_{0-t}, $AUC_{0-\infty}$ and $AUC_{0-\tau}$, half-life $T_{1/2}$, total clearance Cl_t/F, volume of distribution V_d/F, elimination constant k_{el}.
Planned number of research sites and their location	It is planned to involve up to 2 research sites in the Russian Federation.
Design and methodology	This is an open-label prospective non-comparative study to evaluate the safety, tolerability, pharmacokinetics and the effect of food of medicinal product PBTZ169 in 80 mg capsules when used in increasing doses. The study will be divided into 2 stages. ***First stage – dose escalation when used once or twice, effect of food with single administration*** Volunteers who meet the selection criteria for the study will be included in 5 cohorts: ✓ Cohort 1A (C1A) – includes 10 healthy volunteers of the main group, each of whom will receive PBTZ169 only twice: during period 1 of the ***First stage*** of the study on an empty stomach at a dose of 640 mg (8 80 mg capsules once a day) and during period 2 of the ***First stage*** of the study after meal at a dose of 640 mg (8 80 mg capsules, once a day) and 1 healthy backup volunteer.

	✓ Cohort 1A (C1A) – includes 10 healthy volunteers of the main group, each of whom will receive PBTZ169 only twice: during period 1 of the ***First stage*** of the study after meal at a dose of 640 mg (8 80 mg capsules once a day) and during period 2 of the ***First stage*** of the study on an empty stomach at a dose of 640 mg (8 80 mg capsules, once a day) and 1 healthy backup volunteer. ✓ Cohort 2 (C2) – includes 10 healthy volunteers of the main group, each of whom will receive a single dose of PBTZ169 on an empty stomach at a dose of 960 mg (12 80 mg capsules, once a day) and 1 healthy backup volunteer. ✓ Cohort 3 (C3) – includes 10 healthy volunteers of the main group, each of whom will receive PBTZ169 twice on an empty stomach at a dose of 640 mg (8 80 mg capsules, twice daily with a 12-hour interval; total daily dose – 1280 mg) and 1 healthy backup volunteer. ✓ Cohort 4 (C4) – includes 10 healthy volunteers of the main group, each of whom will receive a single dose of PBTZ169 on an empty stomach at a dose of 1280 mg (16 80 mg capsules, once a day) and 1 healthy backup volunteer. Randomization will be done after hospitalization on the day before the first administration of the investigational product (Day 0 of the study) within each cohort by the envelope randomization method. Volunteers of each cohort (C1A, C1B, C2, C3 and C4) will be randomized at a ratio of 10:1: • main therapy group – 10 volunteers who will receive a single dose or two doses of the investigational product; • group of backup volunteers – 1 volunteer who receive one dose or two doses of the investigational product only if one of the volunteers of the main group of this cohort leaves the study before dosing and within 4 hours from the moment of dosing due to a reason unrelated to AE/SAE. Volunteers of the main group and backup volunteers will be hospitalized in the evening on the day before the administration of the product, but at least 12 hours before planned administration of the product. Volunteers of the main group will be hospitalized for about 2.5 days, including the visit on the day of hospitalization, day of administration of the investigational product and 48 hours after the administration of the investigational product. Backup volunteers of cohorts of the ***First stage*** of the study will be discharged from

the hospital at least 4 hours after the administration of the last capsule by the last volunteer of the main group if there will be no need to replace a dropped out volunteer.

Administration of the product will start simultaneously in cohorts C1A and C1B. The use of the product in volunteers of the C2 cohort will begin after the administration of the product by volunteers of the C1A and C1B cohorts. In volunteers of the C3 and C4 cohorts, the product will be used at least 7 days after volunteers from the previous C2 cohort take the investigational product and after obtaining results of safety evaluation of the investigational product (adverse events, changes in vital signs, laboratory test results, ECG and physical examinations) in volunteers of the previous C2 cohort. In volunteers of the C3 and C4 cohorts, the investigational product will be used in case of dose-limiting toxicity (DLT) in less than 50% of volunteers from the C2 cohort.

All volunteers of the C1A and C1B cohorts will take the product on the same day in two periods (1 therapy day in each) between which there will be a carry-over period (≥6 days).

Order	***Number of volunteers***	***Study period***	
		1	***2***
1	10	PBTZ169, 640 mg (8 80 mg capsules), on an empty stomach	PBTZ169, 640 mg (8 80 mg capsules), after a standard meal
2	10	PBTZ169, 640 mg (8 80 mg capsules), after a standard meal	PBTZ169, 640 mg (8 80 mg capsules), on an empty stomach

On an empty stomach the product is administered (by volunteers of cohorts C2 and C4, cohort C1A during period 1, cohort C1B during period 2) after 10 hours of night fasting, washing down 300 mL of bottled water. Each volunteer will administer 4 capsules within 2 minutes broken down into few portions, depending on the total number of capsules, washing down each portion with a few sips of water On the day of administration it is allowed to drink as much water as one wants except for 1 hour prior to administration of the product, during which water consumption is not allowed, and 4 hours after the administration of the product (during the first hour water consumption is not allowed, during the next 3 hours water consumption will be regulated: the volunteer will need to drink 100 mL of bottled water every hour). Within 4 hours after administration, volunteers will not be allowed to eat. 4 hours after administration, volunteers will receive a standard meal.

	After food intake (by volunteers of the C1A cohort – during period 2, of the C1B cohort – during period 1) the medicinal product is administered 30 minutes (± 2 minutes) after the beginning of a standard breakfast, washing down with 300 mL of bottled water (within 2 minutes, 4 capsules broken down into few portions depending on the total number of capsules, washing down each portion with a few sips of water). Breakfast is provided after 10 hours of night fasting. On the day of administration it is allowed to drink as much water as one wants except for 30 minutes prior to administration of the product, during which water consumption is not allowed (except for that present in the breakfast), and 4 hours after the administration of the product (during the first hour water consumption is not allowed, during the next 3 hours water consumption will be regulated: the volunteer will need to drink 100 mL of bottled water every hour). Within 4 hours after administration, volunteers will not be allowed to eat. 4 hours after administration, volunteers will receive a standard meal. Volunteers of the C3 cohort (two administrations) will take the product twice a day, washing down with 300 mL of bottled water each time (within 2 minutes, 4 capsules broken down into few portions depending on the total number of capsules, washing down each portion with a few sips of water). For the first time, volunteers of the C3 cohort will take the medicinal product in the morning on an empty stomach after 10 hours of night fasting, second time – 12 hours after the first administration after 3 hours of fasting. On the day of administration it is allowed to drink as much water as one wants except for 1 hour prior to each administration of the product, during which water consumption is not allowed, and 4 hours after each administration of the product (during the first hour water consumption is not allowed, during the next 3 hours water consumption will be regulated: the volunteer will need to drink 100 mL of bottled water every hour). Within 4 hours after each administration, volunteers will not be allowed to eat. 4 hours after the first administration, volunteers will receive a standard meal. Standard dinner will be offered to volunteers of the C3 cohort no later than 3 hours before the second administration of the medicinal product. Each volunteer in the C1A, C1B, C2 and C4 cohorts will have their venous blood collected to determine the concentration of PBTZ169 and its metabolites before the administration of the product (point 0, blood sample in the range from -5 min to -1 min), and then at the following time points after the administration of the medicinal product: at 0:30, 1:00, 1:30, 2:00, 3:00, 4:00, 6:00, 9:00, 12:00, 24:00, 48:00 and 72:00 (h:min).

	For volunteers of the C3 cohort (two administrations), venous blood will be collected to determine the concentration of PBTZ169 and its metabolites before the first administration of the medicinal product (point 0, blood sample in the range from -5 min to -1 min), and then within 72 hours at the following times points after each administration of the medicinal product: at 0:30, 1:00, 1:30, 2:00, 3:00, 4:00, 6:00, 9:00, 12:00 (the point before the second administration of the medicinal product in the range from -5 min to -1 min), 12:30, 13:00, 13:30, 14:00, 15:00, 16:00, 18:00, 21:00, 24:00, 48:00 , 72:00 (h:min) after the first administration of the medicinal product. During blood sampling for pharmacokinetics before the time point of 48:00 after the administration of the medicinal product, volunteers will be staying in the hospital and will be discharged after all procedures planned by the protocol have been completed, then follow-up will continue on an outpatient basis. After discharge from the hospital, volunteers will visit the research site in 1 day (on Day 4 volunteers of all cohorts and on Day 10 only volunteers of cohorts C1A and C1B). Venous blood samples will be collected from each volunteer at the time point of 72:00 after the administration of the medicinal product and follow-up procedures will be carried out. 5±1 days after the last administration of the medicinal product (on Day 12±1 of the study for volunteers of cohorts C1A and C1B or on Day 6±1 of the study for cohorts C2-C4), volunteers will visit the research site for to undergo procedures of follow-up visit (FUV; safety evaluation). Point 0 before the administration of the medicinal product, including the point before the second administration of the medicinal product, can be within the range from -5 min to -1 min. For time points of 24:00, 48:00, 72:00 after the administration of the medicinal product, deviations of 10 minutes from the specified time are allowed in either direction (±10 min). For all other time points for blood sampling after the administration of the investigational medicinal product, deviations of not more than 2 min in either direction (± 2 min) are allowed. At each time point of blood sampling for the purpose of determination of the concentration of PBTZ169, additional venous blood samples will also be collected for storage for determination of additional parameters should it become necessary. A detailed description of the work with clinical blood samples for the purpose of study of pharmacokinetics will be provided in the instructions prepared by the central laboratory. After the completion of the first part of the study, main samples (blood plasma samples of volunteers) will be sent to the central laboratory to determine the concentration of the investigational

	product PBTZ169 and its two metabolites (MET-11526124 3-OXO MET-11526115 3-OH). Additional samples (blood plasma samples of volunteers) will be stored in the research site in a freezer at a temperature not exceeding -65 °C until the end of the pharmacokinetic part of the study or until further directions from the Sponsor. After the study is completed by the last volunteer from the ***First stage*** (C1A, C1B, C2, C3 and C4), safety and pharmacokinetics, as well as the effect of food will be analyzed based on the data of all cohorts who administered the product once or twice. Based on the results of the evaluation of safety, pharmacokinetics and analysis of the effect of food after the end of the ***First stage***, the Sponsor: ✓ will determine the dose for the study of PBTZ169 with repeated use in Phase 2 of the study. ✓ will decide on the mode of administration of PBTZ169: on an empty stomach or after meal, once a day or twice a day. ✓ can decide to adjust time points for sampling (if necessary, appropriate amendments will be made to the protocol); ✓ can decide to make changes to study procedures at Stage 2 (where necessary, appropriate amendments will be made to the protocol). ***Second stage – repeated administration*** At the second stage, it is planned to recruit 1 cohort consisting of 10 healthy volunteers, to study the medicinal product with repeated use. Volunteers who meet selection criteria for the study will be enrolled in the next cohort for multiple product administration: • Cohort 5 (C5) – includes 10 healthy volunteers, each of whom will receive the medicinal product PBTZ169 at a dose of X[1] mg daily on an empty stomach or after meal, once or twice a day[1] at the same time ±15 minutes for 14 days. It is possible to enroll additional 4 backup volunteer. Backup volunteers will be enrolled as per the decision of the Sponsor only if two or more volunteers from the main group of cohort 5 drop out before Day 7 of the study, for any reason other than AE/SAE, in the same number as there are dropped out volunteers, for which an additional screening will be carried out. Volunteers will be hospitalized in the evening on the day before the administration of the product, but at least 12 hours before planned

[1] The dose of PBTZ169 and the mode of administration of the product (on an empty stomach or after meal, once or twice a day) will be determined by analyzing the data obtained in the first stage.

	administration of the product. Mode of administration of the medicinal product and corresponding restrictions on consumption of food and water will be determined based on the results of the evaluation of safety, pharmacokinetics and analysis of the effect of food with administration of the investigational product once or twice after the ***First stage*** of the clinical study. For volunteers from the C5 cohort, blood for determination of the concentration of PBTZ169 and its metabolites will be collected before and after the administration of the first, 7th and last (14th) dose of the medicinal product at the following time points: 5 minutes before the administration of the medicinal product (only until the first dose), 0 min and within 24 h after the administration of the first, 7th and last (14th) dose of the medicinal product in: 0:15, 0:30, 1:00, 1:30, 2:00, 3:00, 4:00, 6:00, 8:00, 10:00, 12:00, 24:00 (h:min after the administration of a dose of the medicinal product). During days 3-6 and 9-13 of administration of the medicinal product, in order to determine the concentration of PBTZ169, venous blood will be collected daily at 0 min (before the administration of the medicinal product). After the administration of the last (14th) dose of the medicinal product, blood samples will also be collected at 48 h and 72 h points. During the entire time of administration of the medicinal product and before blood collection at 48 h time point after the last administration of the medicinal product, volunteers will be followed-up in a hospital. Then, after all procedures planned under the protocol, volunteers will be discharged, after which they will be followed up on an outpatient basis. Blood sampling at the time point of 72 hours after the last administration of the medicinal product will be done on an outpatient basis. After discharge from the hospital, volunteers from the C5 cohort will have to visit the research site after 2 days to have their blood sampled at the time point of 72 hours, and also 7±1 days after the last administration of the medicinal product (Day 21±1 of the study) to undergo procedure of follow-up visit (FUV, safety evaluation). For the following time points, deviations from the specified time of 10 minutes in either direction are allowed (± 10 min): 24 h after the administration of the first, 7th and last (14th) dose of the investigational product. For time points of 48 and 72 hours after the administration of the last (14th) dose, deviation from the specified time of 20 minutes in either direction (± 20 min) is allowed. For all other time points for blood sampling after the administration of the investigational medicinal product, deviations of not more than 2 min in either direction (± 2 min) are allowed. In case of early drop-out of a volunteer, in the absence of risk for the volunteer, attempts will be made to collect blood samples from them according to schedule for the last (14th) dose of the medicinal product.

	At each time point of blood sampling for the purpose of determination of the concentration of PBTZ169, additional venous blood samples will also be collected for storage for determination of additional parameters should it become necessary. A detailed description of the work with clinical blood samples for the purpose of study of pharmacokinetics will be provided in the instructions prepared by the central laboratory. After the completion of the first part of the study, main samples (blood plasma samples of volunteers) will be sent to the central laboratory to determine the concentration of the investigational product PBTZ169 and its two metabolites (MET-11526124 3-OXO MET-11526115 3-OH). Additional samples (blood plasma samples of volunteers) will be stored in the research site in a freezer at a temperature not exceeding -65 °C until the end of the pharmacokinetic part of the study or until further directions from the Sponsor. ***Follow-up period*** Follow-up of volunteers from cohorts of the ***First stage*** (C1A, C1B, C2, C3 and C4) will be 5±1 days after the last dose of the medicinal product. After discharge from the hospital, volunteers will need to visit the research site 5±1 days after the administration of the medicinal product (on Day 12±1 of the study for volunteers of cohorts C1A and C1B or on Day 6±1 of the study for cohort C2-C4) to undergo procedures of follow-up visit (FUV; safety evaluation), after which the volunteers will end their participation in the study. Total duration of the follow-up period for each volunteer of the C5 cohort (cohort of ***Second stage***) is 7±1 days after the last dose of the medicinal product. After discharge from the hospital, volunteers from the C5 cohort will need to visit the research site 7±1 days after the last administration of the medicinal product (Day 21±1 of the study) to undergo procedures of follow-up visit (FUV; safety evaluation), after which volunteers will end their participation in the study. Maximum duration of participation in the study will be 30 days (for healthy volunteers from cohorts C1A and C1B – 24 days, cohorts C2, C3 and C4 – 18 days, cohort C5 – 30 days).
Justification of dose choice	***Dose selection for single administration*** To date, two clinical studies of PBTZ169 have been completed: Phase I clinical study (protocol No. PBTZ169-Z00-C01-1), where PBTZ169 was first used in humans, and Phase IIa clinical study (protocol No. PBTZ169-A15-C2A-1), where the medicinal product PBTZ169 was used in patients with newly diagnosed respiratory

	tuberculosis with bacterial excretion and preserved sensitivity to isoniazid and rifampicin. Based on the results of analysis of pharmacokinetics of PBTZ169 in these studies, it was decided to further study the product in higher doses in healthy volunteers. The highest dose in the two previous clinical studies of PBTZ169 was 640 mg. The 640 mg dose was well tolerated both by volunteers of the Phase I study and by patients of the Phase IIa study, at a dose of 640 mg the medicinal product had an acceptable safety profile. During the Phase I study, the only case of dose-limiting toxicity (DLT) recorded during the study was related to an increase in blood glucose after a single dose of 80 mg. During the Phase I study, no serious adverse event was recorded. 6 AEs had a relationship with the investigational product, the following AEs were recorded during the study: headache (4 cases in 4 volunteers, *possible relationship*), leukocytosis (1 case in 1 volunteer, *possible relationship*) and increased blood glucose (only 1 case in 1 volunteer, *probable relationship*). In the Phase IIa study, there was one serious adverse event of moderate severity, *without a connection* with the medicinal product – a spontaneous tuberculous-related paraproctitis in one patient (from the group receiving the medicinal product at a dose of 640 mg), which led to withdrawal of the medicinal product and subsequent drop-out of the patient. *Possible relationship* with therapy with the investigational product was suspected in 4 cases of AEs, all of which were in a patient who dropped out of the study due to SAE. In both studies, as the dose increased, no increase in the frequency of AEs was observed. To study the effect of food, in this study it was decided to use the maximum dose that had been studied in the previous two clinical studies (640 mg), which had an acceptable safety profile. Calculation of doses for single use is done based on recommendations provided in Guidelines for Determination of a Safe Dose of Medicinal Product for Phase I Clinical Studies in Adult Volunteers (Guidelines for Pre-Clinical Studies of Medicinal Products, Part One, 2012). ***Determination of no-observed-adverse-effect level (NOAEL) and calculation of human equivalent dose (HED)*** Preclinical study of subchronic toxicity of finished dosage form was done on rats with intragastric administration of the medicinal product at doses of active pharmaceutical ingredient (API) of 9-180 mg/kg/day daily for 30 days. According to study results, NOAEL in rats was 180 mg/kg. Preclinical study of acute toxicity of finished dosage form was done on rats with intragastric administration of the medicinal product at doses of 9-360 mg/kg (API).

	During experiments evaluating the toxicity of the medicinal product in rats, the investigational product had no effect on the appearance, general status, physiological parameters, had no adverse effect on hematological and biochemical indicators of blood and basic physiological functions of the body, did not cause pathomorphological changes. There were no deaths, sex differences and differences from control groups. For rats, a conversion factor of 6 was used for calculating HED. HED, calculated based on NOAEL in rats, was 30 mg/kg [180 (mg/kg)/6]. Maximum dose for this study will be 1280 mg once. The maximum dose can be justified by the absence of a negative effect of the medicinal product when used at doses of API up to 180 mg/kg (HED=30 mg/kg; 2100 mg for a person weighing 70 kg) in rats in the study of subchronic toxicity of the medicinal product, up to 360 mg/kg of API (HED=60 mg/kg; 4200 mg for a person weighing 70 kg) in rats in the study of acute toxicity of medicinal product. Thus, the selected maximum dose of 1280 mg (once or 640 mg twice daily) is in the range of doses studied on animals (rats): 2100 to 4200 mg. Thus, for further study of safety, tolerability and evaluation of pharmacokinetics, 960 mg and 1280 mg doses (once or 640 mg twice daily) were selected. Dose step was selected based on Phase I study, where the dose step was 40 to 320 mg (40 mg, 80 mg, 160 mg, 320 mg and 640 mg). ***Selection of doses and duration of administration for repeated dosing*** Doses of PBTZ169 for repeated administration will be selected based on analysis of data of safety and pharmacokinetics after the end of the study by volunteers from the cohorts of the ***First stage*** (C1A, C1B, C2, C3 and C4). For multiple dosing, it is planned to select a single dose. Primary criterion for dose selection will be good tolerability and safety of the medicinal product administered once or twice at a corresponding dose, including detection of dose-limiting toxicity (DLT) in less than 50% of volunteers from a corresponding cohort administering the product once. It is anticipated that the chosen dose will be the maximum dose within the range studied with single or double administration provided the medicinal product is well tolerated. A decision will also be made on the mode of administration of PBTZ169: on an empty stomach or after meal, once a day or twice a day. Repeated use of PBTZ169 will take place in the hospital under careful monitoring of volunteers. Given that in the subchronic toxicity study and in the chronic toxicity study the duration of

	administration of the product in rabbits and rats was 30 and 180 days respectively, according to Guidelines for Evaluation of Medicinal Products of 2013 (Volume I), duration of administration of 14 days in this clinical study is justified.
Planned number of subjects in the study	***Total number of volunteers:*** it is planned to enroll up to 69 healthy volunteers (10 per each cohort, 60 volunteers in 6 cohorts + 9 possible backup volunteers). Screening – up to 100 volunteers.
Selection criteria	Healthy volunteers, male and female, aged 18-45 years (inclusive) that meet all acceptance criteria.
Inclusion criteria	Volunteers who meet each of the following criteria will be included in the study: 1. Written informed consent from the volunteer. 2. Men and women aged 18-45 years, inclusive. 3. Body mass index of 18.5-30 kg/m^2. 4. Verified "healthy" diagnosis based on physical examination, vital signs, standard laboratory tests (complete blood count and biochemical blood test, urine analysis) and instrumental tests (ECG, fluorography examination or X-ray examination). 5. Negative results of tests for human immunodeficiency virus (HIV), syphilis, hepatitis B (Hbs Ag) and hepatitis C (antibodies to HCV). 6. Ability to comply with all the requirements of the protocol in the opinion of the investigator. 7. Consent of the participant and his/her partner to use reliable contraceptive methods during the study and within 90 days after the end of their participation. A reliable method of contraception is a combination of a male condom with at least one of the following methods: • hormonal contraceptives used by the male's partner (only if she does not participate in this clinical study); • use of aerosols, creams, suppositories and other agents containing spermicides; • use of intrauterine device by female partner.
Exclusion criteria	Volunteers who meet at least one of the following criteria will not be included in the clinical study: 1. History of allergies, including at least one episode of allergy to medications. 2. Chronic diseases of the cardiovascular, bronchopulmonary, neuroendocrine systems, ENT, as well as diseases of the gastrointestinal tract, liver, kidneys, blood, skin. 3. Hypolactasia (lactose intolerance, lactase deficiency) or glucose-galatose malabsorption in medical history. 4. Chronic eye diseases except for myopia, hypermetropia and astigmatism of mild and moderate severity.

	5. Surgeries on the gastrointestinal tract (except for appendectomy done more than 1 year before screening). 6. Regular administration or use (including externally) of hormonal agent for more than 1 week less than 45 days before screening 7. Regular administration of medicinal products less than 4 weeks before screening. 8. Use of medicinal products that have a pronounced effect on liver function or hemodynamics (barbiturates, omeprazole, cimetidine, etc.) less than 30 days before screening. 9. Positive test for narcotics and psychotropic products. 10. Blood pressure after resting in supine position for at least 5 minutes above 130 mm Hg (systolic blood pressure) and 90 mm Hg (diastolic blood pressure) or below 110 mm Hg (systolic blood pressure) and 60 mm Hg (diastolic blood pressure). 11. Heart rate (according to ECG) after resting in supine position for at least 5 minutes above 90 bpm or below 60 bpm. 12. Blood donation (450 mL of blood or plasma and more) less than 3 months before the screening. 13. Acute infectious diseases less than 4 weeks before screening. 14. Administration of more than 10 units of alcohol per week (1 unit of alcohol is equivalent to 500 mL of beer, 200 mL of wine or 50 mL of a spirit) or history of alcoholism, drug abuse, substance abuse. 15. Mental diseases. 16. Smoking for three months before screening. 17. Participation in any clinical study less than 3 months before screening. 18. Planned conception or sperm donation during the study after the administration of the investigational product or within 3 months after the last administration of the product. 19. Positive pregnancy test for women. 20. Breastfeeding period.
Withdrawal criteria	Withdrawal criteria are: 1. Refusal of volunteer to participate in the study at any stage. 2. Developed adverse event, including serious: individual intolerance of the investigational medicinal product, hypersensitivity to components of the medicinal product discovered after administration, making further participation of the volunteer in the study impossible.

	3. Any event or condition of the volunteer that according to the investigator makes further participation of the volunteer in the study impossible. 4. Volunteer's lack of discipline, loss of contact with the volunteer. 5. Use of products containing cytochrome P450 inhibitors, including products containing grapefruit, pomelo, cranberries or their juices 72 hours before the administration of the medicinal product. 6. Use of products containing xanthine or its derivatives (caffeine, theobromine, etc.), including chocolate, tea, coffee or cola 48 hours before the administration of the product and before the end of the study. 7. Vomiting within the first 4 hours after the administration of the medicinal product. 8. Inclusion of the volunteer in the study when he/she does not meet inclusion/exclusion criteria. 9. Use of prohibited therapy. 10. Termination of the study by the Sponsor. 11. Termination of the study by the Investigator. 12. Termination of study by regulatory bodies. 13. Positive pregnancy test (for women). In case a volunteer drops out for any reason, all already collected samples will be analyzed; moreover, investigators will attempt to obtain as much information about the volunteer as possible (including collection of bio-samples and clinical information, unless informed consent is withheld) to ensure his/her safety. In case of a volunteer drops out of the study before dosing and within 4 hours from the moment of dosing (for volunteers from cohorts C1A, C1B, C2, C3 and C4) or until the end of the visit on the 7th day of administration of the medicinal product (for volunteers from the C5 cohort) for the following reasons, in the absence of risk the volunteer may be replaced with a backup volunteer: 1. Refusal of the volunteer to participate in the study. 2. Volunteer's intolerance of study procedures. 3. Any event or condition of the volunteer that according to the investigator makes further participation of the volunteer in the study impossible. 4. Volunteer's lack of discipline (including if the volunteer was admitted to the hospital after designated time), loss of contact with the volunteer (including due to change of residence).

	5. Use of alcohol or products containing grapefruit, pomelo, cranberries or their juices by volunteers 72 hours before the administration of the product and later before the end of participation. 6. Use of products containing xanthine or its derivatives (caffeine, theobromine, etc.), including chocolate, tea, coffee or cola 48 hours before the administration of the product and before the end of the study. 7. Inclusion of the volunteer in the study when he/she does not meet inclusion/exclusion criteria. In cohorts C1A, C1B, C2, C3 and C4 one volunteer can be replaced. In cohort C5, volunteers can only be replaced in the event if two or more volunteers drop out.
Investigational medicinal products	PBTZ169, capsules for oral administration, 80 mg
Dose and route of administration	***Once orally:*** • Cohort C1A – 640 mg (twice in two periods) • Cohort C1B – 640 mg (twice in two periods) • Cohort C2 – 960 mg • Cohort C4 – 1280 mg ***Twice orally:*** • Cohort C3 – 1280 mg (640 mg, twice with an interval of 12 hours) ***Multiple times orally:*** • Cohort 5 – X[2] mg/day (for 14 days)
Duration of the study for each volunteer	The expected duration of participation in the study for each volunteer from cohorts C1A and C1B (studying the effect of food with single administration of PBTZ169) will be 22 to 24 days, including the screening period (10 days), hospitalization day, therapy in the first period of the study (1 day), follow-up between two study periods (≥6 days), therapy in the second study period (1 day) and follow-up (5±1 days after the last dose). Duration of hospitalization of volunteers will be about 2.5 days in each of the two study periods (for cohorts C1A and C1B), including hospitalization day, the day of administration of the investigational product and 48 hours after the administration of the investigational product. After discharge from the hospital in each of the two periods, volunteers from cohorts C1A and C1B will have to visit the research site after 1 day to have their blood collected for pharmacokinetics (72 hours after the administration of the investigational product), and then visit the research site 5±1 days

[2] The dose of PBTZ169 will be determined based on the results of data analysis and taking into account conclusion of the Independent Data and Safety Monitoring Board.

	after the last administration of the product (LA Visit, Day 12±1 study) to undergo procedures of follow-up visit (safety evaluation), after which volunteers will end their participation in the study. Expected duration of participation in the study for each volunteer from cohorts C2, C3 and C4 (PBTZ169 administered once or twice) will be 16 to 18 days, including screening periods (10 days), hospitalization day, therapy period (1 day) and follow-up period (5±1 days after the last dose). Volunteers from cohorts C2, C3 and C4 will be hospitalized for about 2.5 days, including a visit on the day of hospitalization, the day of administration of the investigational product and 48 hours after the administration of the investigational product. After discharge from the hospital, volunteers from cohorts C2, C3 and C4 will have to visit the research site after 1 day to have their blood collected for pharmacokinetics (72 hours after the administration of the investigational product), and then visit the research site 5±1 days after the last administration of the product (LA Visit, Day 6±1 study) to undergo procedures of follow-up visit (safety evaluation), after which volunteers will end their participation in the study. Expected duration of participation in the study for each volunteer of the C5 cohort according to protocol will be from 26 to 30 days (repeated use of PBTZ169), including screening (7 days), hospitalization day, therapy period (14 days) and follow-up after the last administration (7±1 days after the last dose). Volunteers from the C5 cohort will be hospitalized for about 17 days, including the day of hospitalization, the day of administration of the investigational product (14 days) and 48 hours after the last administration of the investigational product. After discharge from the hospital, volunteers from the C5 cohort will need to visit the research site after 1 day to have their blood collected at the 72 h point, as well as in 7±1 days after the last administration of the product (LA Visit, Day 21±1 of the study) to undergo follow-up procedures (safety evaluation), after which volunteers will end their participation in the study.
Primary and secondary variables	***Evaluated safety and tolerability variables*** • Adverse events • Changes in vital signs • Results of laboratory tests (complete blood count, biochemical blood test, urine analysis) • ECG results • Results of physical examination

	Evaluated pharmacokinetic parameters (single or double dosing) • Maximum concentration (C_{max}) • Time to reach the maximum concentration (T_{max}) • Area under the concentration-time curve in the time interval from 0 to time (t) when the last blood sample is collected with a concentration above the limit of quantification (AUC_{0-t}) • Area under the concentration-time curve in the time interval from 0 to infinity ($AUC_{0-\infty}$) • Half-life ($T_{1/2}$) • Total clearance (Cl_t/F) • Volume of distribution (V_d/F) • Elimination constant k_{el} ***Evaluated pharmacokinetic parameters (repeated dosing)*** • Maximum concentration (C_{max}) in the dosing interval • Trough concentration with repeated administration (C_{trough}) • Time to reach the maximum concentration (T_{max}) in the dosing interval • Area under the concentration-time curve in the time interval from 0 to the time (t) of collection of the last blood sample with a concentration above the limit of quantification (AUC_{0-t}) • Area under the concentration-time curve in the time interval from 0 to infinity ($AUC0_{-\infty}$) • Area under the concentration-time curve in the dosing interval ($AUC_{0-\tau}$) • Total clearance (Cl_t/F) • Apparent volume of distribution (V_d/F) • Half-life ($T_{1/2}$) • Elimination constant k_{el} ***Evaluated parameters of relative bioavailability and relative degree of absorption (to evaluate the effect of food with single dosing)*** • Relative bioavailability: $f=AUC_{0-\infty}(T)/AUC_{0-\infty}(R)$; $f'=AUC_{0-t}(T)/AUC_{0-t}(R)$ • Relative degree of absorption $f''=C_{max}(T)/C_{max}(R)$
Statistical methods	For statistical analysis, the following populations are used: • Population of all participants included – will include all participants who were screened and meet the selection criteria. The population will be used for listings and presentation of data on the disposition of participants.

	• Safety population – consists of participants who took the investigational product at least once. The population will be used to analyze and evaluate demographic and other source data, as well as all safety indicators. • Pharmacokinetics evaluation population – consists of all participants who took the investigational product at least once in at least one period and with at least 1 measurement of the concentration of the investigational product above limit of quantification. Measurements of the concentration of the medicinal product will be provided in the listing in this subject population. • Pharmacokinetic parameters evaluation population – consists of all participants with at least one PK parameter evaluated in at least one period. This population will be used for analysis of PK parameters • Population for analysis of relative bioavailability and relative degree of absorption in the analysis of the effect of food – consists of all participants of the PK parameters evaluation population from cohorts C1A and C1B who had at least one PK parameter evaluated in two compared periods. Results of comparison of PK parameters will be presented in this subject population. ***Evaluation of safety parameters*** Safety evaluation will include registration of AE/SAE, vital signs, ECG data, physical examination and laboratory tests in the safety population. All safety parameters will be analyzed using indicators of descriptive statistics (mean, standard deviation, median, minimum and maximum values, number of valid cases – for quantitative variables; absolute number, share, distribution – for qualitative variables. ***Evaluation of pharmacokinetic parameters*** All concentration measurements after administration of the product once or twice and with repeated administration will be tabulated according to time points and therapeutic groups, and also presented in the form of listings. Reasons will be provided for all missing measurements, as well as measurements not included in the pharmacokinetic analysis. Descriptive statistics for measurements of concentration and PK parameters will consist of the mean, standard deviation, median, minimum and maximum values, coefficient of variation (%), number of valid cases (N). For concentration and PK parameters such as C and AUC there will also be geometric mean and geometric coefficient of variation.

	Actual values of sampling time will be used for calculating individual values of PK parameters using non-compartmental analysis. Data on dependency of concentration of the medicinal product from time will be presented graphically for each healthy volunteer, based on actual sampling time. Descriptive statistics and mean PK curves will be presented based on planned sampling time points. Mean and individual PK curves will be presented on an ordinary and semilogarithmic scale. ***Evaluation of relative bioavailability and relative degree of absorption (to evaluate the effect of food with single dosing)*** When evaluating the effect of food on the pharmacokinetics of PBTZ169, tested (T) method of administration will be 8 80 mg capsules after meal, reference (R) method – 8 80 mg capsules on an empty stomach. The study will evaluate relative bioavailability and relative degree of absorption. Changes in PK parameters will be presented descriptively and graphically. After logarithmic conversion, primary PK parameters (C_{max} and AUC) will be analyzed using ANOVA. Obtained point estimations and 90% confidence intervals for the difference between mean values of a PK parameter after its logarithmic transformation (lnT – lnR) are potentiated to obtain a point estimation and corresponding 90% confidence interval limits for the ratio of geometric means (T/R).