A phase 1, single-center, double-blind, placebo-controlled clinical trial to evaluate the safety, tolerability, pharmacokinetics and preliminary efficacy of multiple oral administrations of TNP-2092 Capsules in asymptomatic healthy subjects with Helicobacter pylori infection

Protocol

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Protocol of Study TNP-2092-03

Name of Sponsor Company: TenNor Therapeutics (Suzhou) Limited.	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use Only)
Name of Finished Product: TNP-2092 capsules		
Name of Active Ingredient: TNP-2092		

Title of study: A phase 1, single-center, double-blind, placebo-controlled clinical trial to evaluate the safety, tolerability, pharmacokinetics and preliminary efficacy of multiple oral administrations of TNP-2092 Capsules in asymptomatic healthy subjects with Helicobacter pylori infection

Investigator: Yanhua Ding, The First Hospital of Jilin University

Study center: The study will be conducted in a single center in China.

Publication (Reference): None.

Clinical Phase: 1

Objectives

1) To evaluate the safety and tolerability of multiple oral dose-escalation administrations of TNP-2092 Capsules in asymptomatic healthy subjects with Helicobacter pylori infection.
2) To evaluate the pharmacokinetic characteristics of multiple oral dose-escalation administrations of TNP-2092 Capsules.
3) To explore the preliminary efficacy of TNP-2092 Capsules in eradicating Helicobacter pylori through the ^{14}C urea breath test (UBT).

Methodology

This study is a single-center, randomized, double-blind, placebo-controlled, dose-ascending multiple-dose-administration study. The aim of this study is to evaluate the safety, tolerability, and pharmacokinetic profile of TNP-2092 Capsules in asymptomatic healthy subjects with Helicobacter pylori infection, and to explore the preliminary efficacy of TNP-2092 Capsules in eradicating Helicobacter pylori.

In this study, three dose groups of 100 mg, 300 mg and 600 mg will be set up. The drug will be taken twice a day for 14 consecutive days, and last dose on the morning of Day 15. Fifteen subjects in each of the 100 mg and 300 mg dose groups will be randomized at a ratio of 4:1, with 12 subjects receiving the investigational product and 3 receiving placebo. Ten subjects in the 600 mg dose group will be randomized at a ratio of 4:1, with 8 subjects receiving the investigational product and 2 subjects receiving placebo.

During the trial, blood samples will be collected from the subjects at the specified time points for pharmacokinetic analysis. In the 300 mg group, urine and stool samples will be collected from 7 subjects who are first enrolled in the group for metabolic transformation study.

Plasma sample:

- Blood samples are collected at different time points. Day 1: before the first administration (within 60 minutes), 0.5, 1, 2, 3, 4, 6, 8, 10 and 12 hours after administration; Day 15: before administration (within 60 minutes), 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration; Days 2-14: before the first administration every day (within 60 minutes), the trough concentration is measured to monitor the complete pharmacokinetic changes.
- Urine sample (300 mg BID dose group - for 7 subjects who are first enrolled in the group only):
- Urine samples are collected before administration and 0-6 hours, 6-12 hours, 12-24 hours, 24-48 hours and 48-72 hours after administration on Day 15 for metabolic transformation study.

- Stool sample (300 mg BID dose group - for 7 subjects who were first enrolled in the group only):
- Stool samples are collected within 72 hours after administration on Day 15 for metabolic transformation study.

All of the subjects will be followed up by the ^{14}C-urea breath test (UBT) to evaluate the eradication of Helicobacter pylori.

Number of subjects

It is planned to enroll 40 subjects, eight subjects will be administrated with placebo, and 32 subjects will be administrated with TNP-2092 capsules (12 subjects each with 100 mg or 300 mg, and 8 subjects with 600 mg).

Diagnosis and main criteria for inclusion

Each subject will be required to meet all of the following criteria to be eligible for study enrollment:

1) Those who are fully informed of and understand this study and have signed the Informed Consent Form.
2) Those who are willing to follow and able to complete all the trial procedures.
3) Female subjects of childbearing potential must agree to abstinence or take effective contraceptive measures during the trial and at least 70 days (10 weeks) after administration.
4) Male subjects must agree to abstinence or use condoms as a contraceptive measure during the trial and at least 70 days (10 weeks) after administration.
5) Sex: male or female.
6) Age: 18-45 years, including 18 and 45 years.
7) BMI: 19.0-26.0 kg/m^2, including 19.0 and 26.0 kg/m^2.
8) Those who do not smoke, or have smoked less than 5 cigarettes per day within 3 months before screening; those who do not drink alcohol, or have drunk less than 14 units of alcohol per week (1 unit of alcohol = 360 mL of beer or 45 mL of spirits with 40% alcohol content or 150 mL of wine) within 6 months before screening; those who have not smoked or drunk alcohol within 48 hours before admission to the study site.
9) Subjects whose clinical laboratory test results are within the normal range or whose test results are abnormal but judged by the investigator to be of no clinical insignificance.
10) Those with a positive ^{14}C urea breath test (UBT) result.

Subjects meeting any of the following criteria will be ineligible for study enrollment:

1) Those with an allergic constitution, a history of allergic diseases or a history of drug allergy.
2) Those with a history of alcohol or drug abuse in the past 10 years.
3) Those who have donated blood within 3 months before enrollment.
4) Those with regular use of any prescription/over-the-counter drugs, including vitamins, minerals, nutritional supplements or herbs, within 2 weeks before enrollment and during the study period.
5) Those who have taken any drug that changes the activity of liver enzymes 28 days before taking the investigational product or during the study.
6) Those who have participated in any clinical trials within 3 months before enrollment.
7) Those with a history of eradication of Helicobacter pylori.

8) Those who are suffering or have suffered from digestive tract diseases, including digestive tract ulcer, etc.
9) Those with symptoms or past medical history of cardiovascular, respiratory, urinary, neurological, blood, immune, endocrine system diseases or tumor, mental illness, or any situation which, in the opinion of the investigator, may threaten the safety of the subjects or affect the correctness of the trial results.
10) Those whose blood pressure remains above 140/90 mmHg after retest.
11) Pregnant or lactating women.
12) Those who are HIV positive, syphilis positive, hepatitis B surface antigen positive, hepatitis C antibody positive.
13) Those who have had beverages or foods containing methylxanthine (coffee, tea, coke, chocolate, and energy drinks), grapefruit (fruit juice) and alcohol within 48 hours (2 days) before the clinical study.
14) Other circumstances deemed by the investigator to be unsuitable for the subject to participate in this study.

Investigational product, dose and regimen of administration

Investigational product: TNP-2092 capsules.
Dose and regimen of administration: Subjects will be administrated TNP-2092 capsules orally twice daily at the dose of 100 mg, 300 mg, and 600 mg in the fed state for consecutive 14 days and the last dose in the fed state on the morning of Day 15.

Duration of treatment

Approximately up to 63 days (from signing ICF to the end of the study).

Reference treatment, dose and regimen of administration

Placebo: TNP-2092 placebo capsules.
Dose and regimen of administration: the same regimen as that of TNP-2092 capsules.

Criteria for evaluation

Pharmacokinetics

T_{max}, C_{max}, $t_{1/2}$, $AUC_{0-\infty}$, AUC_{0-last}, AUC_{0-tau}, V_d and CL, $T_{max,ss}$, $C_{max,ss}$, $C_{min,ss}$, $C_{avg,ss}$, $t_{1/2,ss}$, $AUC_{0-last,ss}$, $AUC_{0-tau,ss}$, $AUC_{0-\infty,ss}$, V_{ss}, CL_{ss}, accumulation index, fluctuation index, trough concentration.

Safety

incidence of AEs, the relationship between the drug and AEs, severity of AEs, physical examination, clinical laboratory tests (hematology, blood chemistry, coagulation, and urine test), vital signs (blood pressure, pulse and body temperature) and 12-lead ECG.

Efficacy

^{14}C UBT.

Statistical methods

SAS 9.4 will be used for the statistical analysis.

Sample size simulation

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This study is an early phase exploratory clinical trial, the sample size is not based on statistical hypothesis test. but based on the assessment of safety, PK, and preliminary efficacy in line with similar trails. The sample size of 15 patients in both of the 100 mg and 300 mg dose groups, and 10 patients in the 600 mg group are also appropriate for the purpose of the exploration of the PK profile, safety, and efficacy of TNP-2092 capsules.

Population for analyses

- Full Analysis Set (FAS): all the subjects who have been randomized into groups.
- Safety Analysis Set (SS): all the subjects who have been randomized into groups and received at least one dose of study drug.
- PK Concentration Analysis Set (PKCS): all the subjects who have been randomized into groups, received at least one dose of study drug, and have at least one evaluable blood drug concentration.
- PK Parameter Analysis Set (PKPS): all subjects who have been randomized into groups, have received at least one dose of study drug, and have at least one evaluable pharmacokinetic parameter.

Interim analysis

No interim analysis is planned.

PK analysis

Pharmacokinetic analysis will be based on the PKPS. Pharmacokinetic concentration and parameters will be subjected to descriptive analysis by dose group. The mean and individual drug-time curves will be shown graphically. Numbers will include individual values and mean values. In addition, individual and mean dose standardization parameters will be plotted against the dose to evaluate whether there are any obvious trends.

Safety and tolerability analysis

It will be based on the SS. Physical examination results and changes, laboratory test results and changes, vital signs results and changes, as well as ECG results and changes will be descriptive analyzed by dose group and planned time point. The abnormal results of these examinations will also be listed. Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by treatment group and dose according to the system organ class (SOC) and preferred terms (PTs). In addition, serious adverse events (SAEs) and AEs leading to dropout and death will be listed separately.

Efficacy analysis

The preliminary Helicobacter Pylori eradication efficacy will be analyzed based on FAS. The number and percentage of subjects with ^{14}C UBT negative at the follow-up visit will be listed by dose group. Fisher's exact test was used for comparison of percentages between groups (if infeasible for data reasons, summarize only). For all measurements, the baseline values and changes from baseline will be summarized by dose group and visit. Changes from baseline will be compared between groups by visit using analysis of covariance model, with baseline value as covariate and treatment group as fixed effect factors. Missing values will be imputed using last observation carry forward (LOCF). Sensitivity analysis will be performed using mixed model for repeated measures (MMRM), with baseline value and treatment group as fixed effect factors. An unstructured covariance matrix will be preferred in the model, if not fitted, other suitable covariance matrix would be used.

Appendix 1 Study Flowchart

Procedure	Screening visit (Day -14 to Day -3)	Day -2	Day -1	Day 1	Day 2-14	Day 15	Day 16	Day 17	Day 18	Follow-up During Day 4 - 49 [1]
Screening										
Sign the ICF	X									
Demographics	X									
Medical and surgical history	X	X								
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Chest X-ray	X									
Hepatitis B and hepatitis C tests [17]	X									
Syphilis test	X									
HIV test	X									
Alcohol breath test		X								
Drug test		X								
Blood pregnancy test [2]	X		X						X	
Verification of inclusion and exclusion criteria	X	X	X							
^{14}C urea breath test (UBT)	X						X[3]			X
Abdominal ultrasound (digestive system)	X									
Fibro Touch test	X									
Admission		X								
Randomization			X							
Tolerability evaluation										
Hematology/blood biochemistry/coagulation [4]	X		X[5]		X(pre- Day 2,4,6,8,12)				X(72 h)[11]	

Procedure	**Screening visit (Day -14 to Day -3)**	**Day -2**	**Day -1**	**Day 1**	**Day 2-14**	**Day 15**	**Day 16**	**Day 17**	**Day 18**	**Follow-up During Day 4 - 49 [1]**
Urinalysis [4]	X		X[5]		X(pre-Day 2,4,6,8,12)				X(72 h)[11]	
Stool routine [4]	X		X[6]		X(Day 2,4,6,8,12)[7]				X[8]	
Physical examination [4]	X	X			X(Day 4,6,8,12)				X	
12-lead ECG [4]	X	X[14]		X(pre-60 min；post 6h）[10]		X(pre-60 min; post 6h)[11]			X(72 h)[11]	
Vital signs [4]	X	X[14]		X(pre-60 min；post 0.5,2,4,8,12 h）[10]	X(pre-60 min)	X(pre-60 min; post 0.5,2,4,8,12 h)[11]	X(24 h)[11]	X(48 h)[11]	X(72 h)[11]	
Monitoring and recording of adverse events [9]	X	X	X	X	X	X	X	X	X	X
PK sample collection [4]										
Blood samples				X(pre-60 min; post 0.5,1,2,3,4,6,8,10,12 h）[10]	X (pre-60 min)	X(pre-60 min; post 0.5,1,2,3,4,6,8,10,12,16 h）[11]	X(24,36 h)[11]	X(48 h)[11]	X(72 h)[11]	
Urine samples [18]						X	X	X	X	
Stool samples [18]						X	X	X	X	
Investigational product distribution										
Administration [12]				X	X	X[13]				
Standard breakfast and dinner			X	X	X	X	X	X	X[15]	
Discharge from the study site									X	
Follow-up										X[16]

Abbreviations: PK = pharmacokinetics; Pre = before the first daily dose; Post = after the first daily dose;

1. If a subject prematurely terminates the study after taking the drug, subsequent designated visits should be completed.
2. Pregnancy test may be repeated during the course of the study, if deemed necessary by the investigator.

3. UBT is performed before breakfast on Day 16.
4. If multiple assessments are performed at the same time, it is recommended to collect samples/data in the following order in the non-emergency state (but subject to actual clinical practice): PK samples, ECGs, and vital signs; and then all the other assessments. ECGs, blood pressure, and pulse should be measured after the subject has rested for approximately 5 minutes. The subjects are required to fast overnight for 10 hours before blood biochemistry test; water was deprived for 1 hour before administration and 2 hours after administration.
5. If hematology, urinalysis, blood chemistry, and coagulation tests were performed within 48 hours of screening, the results could be used as baseline values and no additional tests were required.
6. If stool routine test was performed within 7 days of screening, the result could be used as the baseline value and no additional tests were required.
7. If no stool specimen was collected on the specified day, the situation should be stated, and no additional collection was required.
8. If no stool specimen was collected on that day, no additional collection was required.
9. Adverse events should be followed up until they are resolved or until the investigator assesses the subject as having returned to baseline.
10. Sampling/testing time (hours) was relative to the time of the first dose on the very day of the study.
11. Sampling/testing time (hours) was relative to the dosing time on Day 15 of the study.
12. Subjects received the drug orally twice daily after breakfast and dinner (the meals should be finished within 30 minutes and the drug should be administered 30 minutes after the start of the meal) with 240 mL of warm water, 12 hours apart. The initial dose was 100 mg twice daily after meals. After the administration for the 100 mg dose group and the evaluation of safety and tolerability were completed, the next dose group would be tested according to the principle of ascending until the maximum dose was reached or the predefined indication for study suspension occurred.
13. The last dose was given 30 minutes after the start of breakfast on Day 15.
14. The 12-lead ECG and vital signs measured before administration on D1 were used as baseline values.
15. Subjects only had breakfast that day.
16. Subjects were required to be in a fasting condition in the morning for the follow-up examinations at the clinical study site.
17. Hepatitis B tests included hepatitis B virus surface antigen (HBsAg), hepatitis B virus surface antibody (HBsAb), hepatitis B virus e antigen (HBeAg), hepatitis B virus e antibody (HBeAb), and hepatitis B virus core antibody (HBcAb). The hepatitis C test is a hepatitis C virus antibody test.
18. Specimens were collected from the first 7 subjects enrolled in the 300 mg dose group.