A phase 1, single-center, double-blind, placebo-controlled clinical study to evaluate the safety, tolerability, and pharmacokinetics of TNP-2092 Capsules, and the food effect on the pharmacokinetics of TNP-2092 Capsules after single-dose oral administration in healthy subjects.

Protocol

Protocol No.: TNP-2092-01

Approval Date: 19 May 2016

ClinicalTrials.gov ID: NCT06178718

Protocol Synopsis of Study TNP-2092-01

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 study to evaluate the safety, tolerability, and pharmacokinetics of TNP-2092 Capsules, and the food effect on the pharmacokinetics of TNP-2092 Capsules after single-dose oral administration in healthy subjects

Investigator: Yanhua Ding, The First Hospital of Jilin University

Study center: A single center.

Clinical Phase: 1

Objectives

1) To evaluate the safety and tolerability of TNP-2092 Capsules in healthy subjects after single-dose escalated oral administration.
2) To evaluate the pharmacokinetic characteristics of TNP-2092 Capsules.
3) To evaluate the effect of eating on the pharmacokinetics of TNP-2092 Capsules after single-dose oral administration in healthy subjects.

Methodology

This is a single-center, randomized, double-blind, placebo-controlled, dose-ascending single-dose-administration study, and a study on the food effects on pharmacokinetics. Five dose groups of 100 mg, 200 mg, 400 mg, 800 mg, and 1200 mg will be set up.

The 100 mg, 200 mg, 800 mg, and 1200 mg groups will complete the single administration clinical study, with 10 subjects randomized in each group, 8 subjects receiving TNP-2092 and 2 receiving placebo. The drug will be administered once in each group in the fasting state, and tolerability will be evaluated on D4. Subjects were sequentially enrolled into different dose groups in ascending order of dose, and only when the previous lower dose was confirmed to be safe and well tolerated could they be enrolled into the next higher dose group.

The 400 mg group will complete the clinical study on single administration and the effects of eating on pharmacokinetics and undergo the metabolic transformation evaluation. A total of 18 subjects will be enrolled in the group and randomized into Group A and Group B, with 8 subjects receiving the investigational product and 1 receiving placebo. The drugs will be administered in the fasting state and in the fed state for two cycles, with a wash-out period of 4 days. In terms of the administration sequence, Group A will first take TNP-2092 Capsules or placebo in the fasting state, and then TNP-2092 Capsules or placebo in the fed state; Group B will first take TNP-2092 Capsules or placebo in the fed state, and then TNP-2092 Capsules or placebo in the fasting state. Tolerability evaluation will be conducted on D4 and at the end of the study of food effects on pharmacokinetics (D8).

The study of the 400 mg group is conducted on the premise that the tolerability evaluation result of the 200 mg group is favorable. After that, if the tolerability evaluation result in the 400 mg group is favorable for the first cycle, the second-cycle clinical study of the 400 mg group and the 800 mg group could be conducted in parallel.

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During the study, blood samples will be collected from the subjects at the specified time points and used for pharmacokinetic analysis. Also, urine and stool samples will be collected from Group A in the 400 mg group in the first cycle for the metabolic transformation study.

- Plasma sample
  - 100 mg, 200 mg, 800 mg and 1200 mg dose groups: For each group, samples are collected before the first (D1) administration (within 15 minutes), and 0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 10 h, 12 h, 16 h, 24 h, 36 h, 48 h and 72 h after administration, with 4 mL collected at each time point.
  - 400 mg dose group
    - Day 1: Before administration (within 15 minutes), and 0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 10 h, 12 h, 16 h, 24 h, 36 h, 48 h and 72 h after administration.
    - Day 5: Before administration (within 15 minutes), and 0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 10 h, 12 h, 16 h, 24 h, 36 h, 48 h and 72 h after administration.
- Urine sample
  - Group A of the 400 mg dose group: Urine samples are collected at 0 h before administration on D1, and 0-6 h, 6-12 h, 12-24 h, 24-48 h and 48-72 h after administration.
- Stool sample
  - Group A of the 400 mg dose group: Stools are collected whenever available within 72 hours after administration on D1.

Number of subjects

It is planned to enroll 58 subjects. Ten subjects will be administrated with placebo, and 48 subjects will be administrated with TNP-2092 capsules (8 subjects each with 100 mg, 200 mg, 800 mg or 1200 mg and 16 subjects with 400 mg).

Diagnosis and main criteria for inclusion

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

1) Adult males or females
2) Eighteen to 45 years of age, inclusive
3) BMI: 19.0-26.0 kg/m^2， including 19.0 and 26.0 kg/m^2
4) 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
5) 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
6) Subjects whose clinical laboratory test results are within the normal range or abnormal tests are judged to be no clinical insignificance by the investigator
7) 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
8) Those who are fully informed of and understand this study, and have signed the Informed Consent Form
9) Those who are willing to follow and able to complete all the trial procedures

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

1) Those with symptoms or medical history of cardiovascular, digestive, respiratory, urinary, neurological, blood, immune, endocrine system diseases or tumor, mental illness, or any condition which, in the opinion of the investigator, may threaten the safety of the subjects or affect the correctness of the trial results
2) Pregnant or lactating women
3) Those whose blood pressure is above 150/90 mmHg or below 85/55 mmHg (supine position)
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 are HIV positive, syphilis positive, hepatitis B surface antigen positive, hepatitis C antibody positive, and/or with a positive drug urine test result
6) Those who have a history of alcohol or drug abuse in the past 10 years
7) Those with an allergic constitution, a history of allergic diseases or a history of drug allergy
8) 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
9) Those who have taken any drug that changes the activity of liver enzymes 28 days before taking the investigational product or during the study
10) Those who have donated blood within 3 months before enrollment
11) Those who have participated in any clinical trials within 3 months before enrollment
12) Those who are the staff of the study site directly affiliated to this study or are their immediate family members. Immediate family members are defined as spouses, parents, children or siblings, whether related by blood or legally adopted
13) Those who are employees of TenNor Therapeutics
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: the doses were 100 mg, 200 mg, 400 mg, 800 mg, and 1,200 mg. For the administration in the fasted state, subjects are required to fast overnight for at least 10 hours and to take capsule with 240 ml of warm water. For the administration in the fed state, subjects are required to fast overnight for at least 10 hours and take high-fat meal 30 min before receiving capsule with 240 mL warm water. Meals should be controlled to finish just before administration.

Duration of treatment

Approximately up to 22 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

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T_{max}, C_{max}, $t_{1/2}$, $AUC_{0-\infty}$, AUC_{0-t}, the amount of drug excreted in the urine at 72 hours after administration (Ae_{0-t}), the amount of drug excreted in feces at 72 hours after administration (Ae_{0-t}), the cumulative drug excretion rate in urine, the cumulative drug excretion rate in feces, and CL.

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

Not applicable.

Statistical methods

SAS 9.4 will be used for the statistical analysis.

Sample size simulation

This study is a early phase exploratory clinical trial, and the sample size was not based on statistical hypothesis test. Study sample size is chosen based on the assessment of safety, PK, and preliminary efficacy in line with similar trails. The sample size of 10 subjects per group, and additional 8 subjects in the 400 mg group for food effect study are also appropriate for the purpose of the exploration of the PK profile and safety of TNP-2092 capsules.

Population for analyses

- Full Analysis Set (FAS): all the subjects who were 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.
- Bioequivalence Set (BES) of food effect: All subjects with no significant protocol violations, no protocol deviations that had impact on PK endpoints (e.g., AUC, C_{max}), who must have received at least one cycle of treatment in the crossover study and have at least one evaluable pharmacokinetic parameter.

Interim analysis

No interim analysis is planned.

PK analysis

PK parameters will be estimated by non-compartmental method using WinNonlin 6.4. 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.

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Food effect analysis

The bioequivalence evaluation principle will be used to evaluate whether food affects the bioavailability of TNP-2092 Capsules. That is, if compared with the PK parameters of TNP-2092 Capsules in the fasting state, the 90% confidence intervals of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of TNP-2092 Capsule in the fed state are within 80.00% - 125.00% of the corresponding PK parameters, it can be considered that there is no significant difference in the main pharmacokinetic parameters between the two modes of administration, i.e., food has no effect on the pharmacokinetics of TNP-2092 Capsules. The main pharmacokinetic parameters (AUC and C_{max}) are subjected to variance analysis after log transformation, and the geometric mean ratios of AUC_{0-last}, AUC_{0-inf}, C_{max} and their 90% confidence intervals are calculated under the postprandial and fasting administration modes.

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 subjected to descriptive analysis by dose group and planned time point. The abnormal results of these examinations will also be listed. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), and summarized by treatment group and dose according to the system organ class and preferred terms. In addition, serious adverse events and adverse events leading to dropout and death will be listed separately.

Efficacy analysis

Not applicable.

Appendix 1 Study Procedures - 1 (100 mg, 200 mg, 800 mg, and 1200 mg groups)

Study procedures	Screening visit[1] (Day -14 to Day -2)	100 mg, 200 mg, 800 mg and 1200 mg groups				
		Day -1	Day 1	Day 2	Day 3	Day 4
Screening						
Signing of ICF	X					
Demography	X					
Medical and surgical history	X	X				
Concomitant medications	X	X	X	X	X	X
Chest X-ray	X					
Hepatitis B and hepatitis C tests	X					
Syphilis test	X					
HIV test	X					
Alcohol and drug test	X	X				
Blood pregnancy test	X	X				X
Verification of inclusion and exclusion criteria	X	X				
Admission		X				
Randomization		X				
Tolerability Assessment						
Clinical laboratory tests (hematology, blood biochemistry, coagulation, urinalysis, and stool routine) [2]	X	X[3]		X (24 h)		X (72 h)
Physical examination[2]	X	X				X
12-lead ECG[2]	X	X	X（pre-60 min[4]; post 0.5,2,4,8,12 h）	X (24 h)	X (48 h)	X (72 h)
Vital signs[2]	X	X	X（pre-60 min[4]; post 0.5,2,4,8,12 h）	X (24 h)	X (48 h)	X (72 h)

Study procedures	**Screening visit[1] (Day -14 to Day -2)**	**100 mg, 200 mg, 800 mg and 1200 mg groups**				
		Day -1	**Day 1**	**Day 2**	**Day 3**	**Day 4**
Monitoring and recording of adverse events	X	X	X	X	X	X
PK sample collection[2, 5]						
Blood samples			X（pre-15 min; post 0.5,1,2,3,4,6,8,10,12,16 h）	X (24,36 h)	X (48 h)	X (72 h)
Clinical study drug dispensing						
Drug administration			X			
Discharge from the study site						X

Abbreviations: pre = pre-dose; post = post-dose

1. Subject screening is performed within 14 days prior to the first dose (Day 1), with the same screening procedure for each group;
2. If multiple assessments are to be performed at the same time, samples/data should be collected in the following order in the non-emergency state: PK sample, 12-lead ECG, vital signs, followed by all other assessments. 12-lead ECG, blood pressure, and pulse should be measured after the subject has rested in supine position for approximately 5 min;
3. If clinical laboratory tests are performed within Day -2 at screening, the results could be used as baseline values and no additional tests are required.
4. The values of 12-lead ECG and vital signs measured before administration on Day 1 are taken as the baseline values;
5. Based on the results of the analysis of the pharmacokinetic data of the 100 mg group, fine adjustments may be made to the frequency and number of blood collections for the dose groups to be tested.

Appendix 2 Study Procedures - 2 (400 mg group)

Study procedures	Screening visit[1] (Day -14 to Day -2)	400 mg group								
		Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
Screening										
Signing of ICF	X									
Demography	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	X									
Syphilis test	X									
HIV test	X									
Alcohol and drug test	X	X								
Blood pregnancy test[2]	X	X								X
Verification of inclusion and exclusion criteria	X	X								
Admission		X								
Randomization		X								
Safety assessment										
Clinical laboratory tests (hematology, blood biochemistry, coagulation, urinalysis, and stool routine)[2]	X	X[3]		X (24 h)		X (72 h)		X (24 h)		X (72 h)
Physical examination[2]	X	X				X				X

Study procedures	Screening visit[1] (Day -14 to Day -2)	400 mg group								
		Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
12-lead ECG[2]	X	X	X（pre-60 min[4]; post 0.5,2,4,8,12 h）	X (24 h)	X (48 h)	X (72 h)	X（pre- 60 min[4]; post 0.5,2,4,8,12 h）	X (24 h)	X (48 h)	X (72 h)
Vital signs[2]	X	X	X（pre-60 min[4]; post 0.5,2,4,8,12 h）	X (24 h)	X (48 h)	X (72 h)	X（pre-60 min[4]; post 0.5,2,4,8,12 h）	X (24 h)	X (48 h)	X (72 h)
Monitoring and recording of adverse events	X	X	X	X	X	X	X	X	X	X
PK sample collection										
Blood samples[2, 5]			X（pre-15 min; post 0.5,1,2,3,4,6,8,10,12,16 h）	X (24,36 h)	X (48 h)	X (72 h)	X（pre-15 min; post 0.5,1,2,3,4,6,8,10,12,16 h）	X (24,36 h)	X (48 h)	X (72 h)
Urine samples[2, 5, 6]			X	X	X	X				
Stool samples[2, 5, 6]			X	X	X	X				
Clinical study drug Dispensing										
Drug administration			X				X			
Discharge from the study site										X

Abbreviations: pre = pre-dose; post = post-dose

1. Subject screening is performed within 14 days prior to the first dose (Day 1), with the same screening procedure for each group;
2. If multiple assessments are to be performed at the same time, samples/data should be collected in the following order in the non-emergency state: PK sample, 12-lead ECG, vital signs, followed by all other assessments. 12-lead ECG, blood pressure, and pulse should be measured after the subject has rested in supine position for approximately 5 min;
3. If clinical laboratory tests are performed within Day -2 at screening, the results could be used as baseline values in Cycle 1 and no additional tests are required.
4. The values of 12-lead ECG and vital signs measured before administration on Day 1/Day 5 are taken as the baseline values in Cycle 1 and Cycle 2, respectively;
5. Based on the results of the analysis of the pharmacokinetic data of the 100 mg group, fine adjustments may be made to the frequency and number of blood collections for the dose groups to be tested;
6. Urine and stool samples are collected from subjects in Group A of the 400 mg group for the metabolic transformation study.