Diabetes, Metabolic Syndrome and Obesity

Dovepress
open access to scientific and medical research

Open Access Full Text Article

STUDY PROTOCOL

Randomized, Double-Blind, Placebo-Controlled, Phase I, Dose- Escalation Study to Evaluate the Tolerance, Pharmacokinetics, Pharmacodynamics and Immunogenicity of PEGylated Urate Oxidase for Injection in Healthy Adults and Hyperuricemia Volunteers: Study Protocol

Feifei Sun[1,*], Chenjing Wang[1,*], Yi Xu[1], Pingping Lin[1], Yaozhong Cao[2], Jiahui Zhang[3], Xin Li[1], Xin Jiang[1], Yao Fu[1], Yu Cao[1]

[1]Clinical Trials Center, The Affiliated Hospital of Qingdao University, Qingdao, Shandong, People's Republic of China; [2]Clinical Medical Center, Xiuzheng Pharmaceutical Group, Hangzhou, Zhejiang, People's Republic of China; [3]Xiuzheng Bio-Medicine Research Institute, Hangzhou, Zhejiang, People's Republic of China

*These authors contributed equally to this work

Correspondence: Yu Cao, Clinical Trials Center, The Affiliated Hospital of Qingdao University, Qingdao, Shandong, People's Republic of China, Tel +86 532 82911767, Email caoyu@qdu.edu.cn

Introduction: Hyperuricemia is a disease with abnormal purine metabolism, which leads to the increase of urate concentration. It is an independent risk factor for the occurrence and development of metabolic syndrome, type 2 diabetes, hypertension, cardiovascular disease, chronic kidney disease, and gout. The enzyme urate oxidase can metabolize urate to allantoin, resulting in decreased urate concentrations. Pegylated the urate oxidase can extend half-life and decrease immunogenicity of the protein. This trial aims to evaluate the safety, tolerability, pharmacokinetics(PK), pharmacodynamics(PD) and immunogenicity of a new intravenous PEGylated urate oxidase produced by Xiuzheng Bio-Medicine Research Institute Co., Ltd.

Methods and Analysis: A randomized, double-blind, placebo-controlled, phase I, dose escalation study will be conducted in China. In total, 56 subjects will be enrolled in the study, with 24 healthy subjects in the low dose-escalation stage and 32 patients with hyperuricemia in the high dose-escalation stage. There is a bridging between the two stages. Subjects are randomized to PEGylated urate oxidase or the placebo in a 3:1 ratio in each group and followed up for 71 days observation. The primary outcomes include PK, PD, tolerability; the secondary outcomes include safety and immunogenicity.

Ethics and Dissemination: The trial is performed abiding by the Declaration of Helsinki, Good clinical practice (GCP) and the guidelines of China National Medical Products Administration (NMPA). Relevant documents, including protocol, informed consent and drug inspection report, are all approved independently by the Medical Ethics Committee of the Affiliated Hospital of Qingdao University. The first subject was enrolled on January 17, 2022.

Trial Registration: Clinicaltrials, NCT05226013 (Registered April 2, 2022, Retrospectively registered). ChinaDrugTrials, CTR20211801(Registered July 27, 2021).

Keywords: PEGylated urate oxidase, healthy volunteers, patients with hyperuricemia, study protocol

Introduction

Hyperuricemia is a disease with abnormal purine metabolism which is closely related to metabolic syndrome, type 2 diabetes, hypertension, cardiovascular disease, chronic kidney disease, gout, etc.[1] The current clinical applications of uric

Received: 10 August 2023
Accepted: 19 December 2023
Published: 28 December 2023

acid lowering drugs mainly include drugs that inhibit uric acid production and drugs that promote uric acid excretion.[2] Unfortunately, a proportion of patients with hyperuricemia or gout are very difficult to treat, and therapeutic options for them are limited.[3]

Urate oxidase can oxidize uric acid to allantoin, making it easier to be discharged from the body. Humans lack active urate oxidase, so uric acid is the final product of purine metabolism.[4] Pegloticase, a recombinant pegylated uricase, has been approved by the US Food and Drug Administration for the treatment of refractory gout. Currently, only KRYSTEEXXA® is listed for PEGylated urate oxidase which has not yet been imported and registered in China, and there are no similar formulations available for sale in China.

In this study, we aim to evaluate the safety, tolerance and immunogenicity of PEGylated Urate Oxidase for injection in healthy subjects and hyperuricemia patients.

Methods and Analysis

Study Design

This study is a randomized, double-blind, single center, placebo-controlled, Phase I clinical study conducted in Chinese healthy adults and patients with hyperuricemia to observe the tolerance, PK/PD characteristics, safety and immunogenicity of PEGylated urate oxidase administered by single intravenous injection. A total of 54 subjects will be enrolled in this study, including 24 healthy subjects and 32 patients with hyperuricemia. They are divided into six dose groups, the low dose groups (0.5mg, 1mg, 2mg) for healthy subjects, and the high dose groups (2mg, 4mg, 8mg, 12mg) for patients with hyperuricemia. There are 8 subjects in each group, with 6 receive the test drug, and 2 receive the placebo. We will observe for 22 days for PK and PD, and for 71 days for safety and immunogenicity. Each subject will receive only one dose (experimental drug or placebo). Each group adopts a sentinel administration design. Among the 8 subjects, 2 subjects will be randomly assigned as sentinel subjects, one will receive the text drug and the other will receive placebo. If no serious medical events are found within 48 hours, the observation study of drug administration to other subjects in this group will be conducted. Refer to Figure 1 for details.

Dosing Rationale

The preclinical trial data show that the long-term toxic NOAELs of rats and crab eating monkeys are 4.5mg/kg and 2mg/kg, respectively. According to the body surface area method, the equivalent doses in humans (assuming a human weight of 60 kg) are 45 and 40mg, and a safety factor of 10 is set, which estimates the maximum safe initial dose in humans as

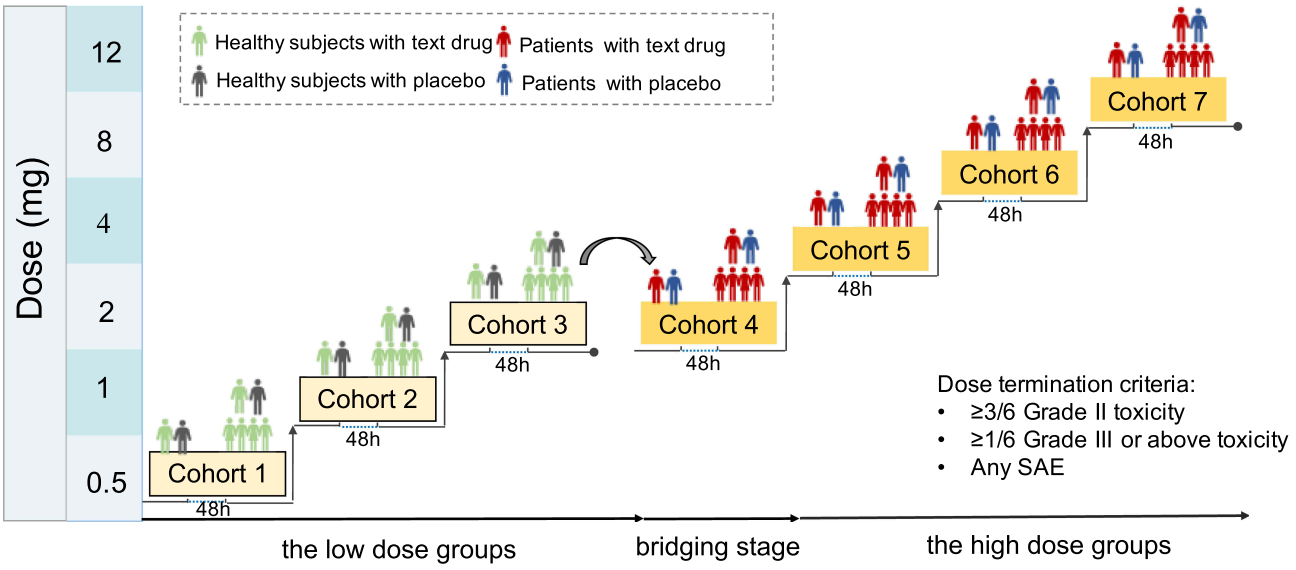

Figure 1 Schematic overview of the dose-escalation stage.

4mg. Referring to similar drugs already on the market (assuming the potency of the study drug is equivalent to that of foreign similar drugs), the initial dose is 0.5mg, and slight pharmacological activity can be observed at this dose. Based on the comprehensive safety and efficacy results, this study ultimately chose 0.5mg as the starting dose for the experiment. Referring to the dose setting of similar drug-related studies and the purpose of fully observing drug safety, 12mg is tentatively selected as the highest dose for the experiment. The study dose was designed to be 0.5, 1, 2, 4, 8, and 12 mg, facilitating the acquisition of comprehensive PK/PD features.

Dose Escalation

This study will be conducted at low doses (0.5, 1 and 2 mg) in healthy people, while at high doses (2, 4, 8 and 12 mg) in patients with hyperuricemia. The 2 mg dose group was conducted in both healthy people and patients to compare PK/PD characteristics in healthy people and patients.

Criteria for the Study Termination

When the safety and efficacy evaluations during the dose increase process meet the termination criteria, it is necessary to communicate and discuss with the researcher and sponsor before deciding whether to stop the dose exploration. The dose termination criteria should be: If 3/6 or more of the subjects in each dose group experience any Grade II toxicity, or 1/6 or more of the subjects experience any Grade III or above toxicity (according to the CTCAE version 5.0 adverse reaction grading standard), the trial will be terminated; If there is any serious adverse event (SAE) related to the study drug during the trial, the trial needs to be suspended. The researcher and the sponsor discuss and analyze the reasons together and determine the impact on subsequent trials.

Subjects Population

All subjects' age between 18 and 60 years old (including the critical value), with the body mass index in the range of 18–30kg/m^2 (including the critical value). The weight of male is ≥50 kg, and that of female is ≥45 kg. Individuals with G6PD deficiency will be excluded. Serum uric acid of heathy volunteers should <360 μ mol/L twice on different days. Patients with hyperuricemia stop uric acid lowering treatment for at least 7 days and 480≤UA≤540μmol/L twice on different days within 7 days.

Randomization and Blinding

Once signed the informed consent, the subjects obtain the screening number according to the screening sequence. This is a randomized, double-blind, placebo-controlled design, using a stratified block randomization method. Each dose group is randomly assigned, and a random number and its corresponding group are generated by SAS version 9.4 or above. Sentinel administration is used in this study, and the first 2 eligible subjects are selected in a 1:1 ratio, and the last 6 subjects are given PEGylated urate oxidase or placebo in a 5:1 ratio. Each qualified subject will receive the randomization number and its corresponding drug (PEGylated urate oxidase or placebo) from small to large according to the screening number.

Combination Therapy

In case of acute gout attack in hyperuricemia subjects, remedial drugs can be used. The specific mode of administration is as follows: the first dose of colchicine is 1mg, 0.5mg is added after 1h, and 0.5mg qd or bid is changed after 12h. In the course of the study, any use of treatments for hyperuricemia and gout such as febuxostat, allopurinol, benzbromarone, are not permitted. Once used, the subject should withdraw from the study and continue to maintain the original medical scheme. For chronic diseases such as hypertension, hyperlipidemia, chronic obstructive pulmonary disease, and coronary heart disease, the original treatment plan should be maintained and truthfully recorded in the combined medication column; the participants are required to consult the investigator when using any other drugs or dietary supplements. When the subject experiences AE or even SAE and requires medical measures, the researcher should record the treatment and medication process, including usage, dosage, duration truthfully.

Evaluation Criteria for Outcome

The safety and tolerability evaluation criteria will include adverse events (the severity of the adverse events will be graded according to the CTCAE version 5.0 adverse reaction grading standard), laboratory tests, vital signs, physical examinations and electrocardiograms.

The PK evaluation criteria will include C_{max}, AUC_{0-t}, AUC_{0-C}, T_{max}, $t_{1/2z}$, V_z, CL_z, λ_z, MRT_{0-t}, $MRT_{0-\infty}$ and $AUC_{\%Extrap}$ in SAD and $C_{max,ss}$, $AUC_{0-t,ss}$, AUC0-∞,ss, AUC_{ss}, C_{av}, T_{max}, $t_{1/2z}$, V_z, CL_{ss}, λ_z, $AUC_{\%Extrap}$, $MRT_{0-\infty,ss}$ and R_{ac} in MAD. The immunogenicity evaluation criteria will include the antidrug antibody positive rate before and after administration.

Statistical Analysis

The number of observations, mean, standard deviation, median, minimum, maximum and CV% of each PK and PD parameter will be summarized by treatment group and gender. The dose–exposure relationship between dose and PK parameters including C_{max}, AUC_{last} and AUC_{inf} will be presented with scatter plot, and then statistically assessed using power model. The change from baseline of blood uric acid, urine uric acid, allantoin and urine creatinine after dosing will be calculated using the scheduled sampling time. PD parameters of blood uric acid, urine uric acid, allantoin and urine creatinine will be calculated using Phoenix WinNonlin 7.0 with non-compartment mode. The dose–response relationship between dose and PD parameter including AUEClast, and Emax will be presented with scatter plot. This is a population PK model informed early-phase clinical study with seamless expansion cohort design. Using dynamic analysis and expansion cohort approach, several study objectives will be seamlessly combined and fulfilled in one single study, especially in patients with hyperuricemia, multi-dose tolerability and PK/PD study will be immediately afterwards initiated when subject blood uric acid reaches the target level in high single-dose group. In single-dose study, NONMEN version 7.2 will be used to perform population PK/PD modelling and simulation, CV will be calculated and some key covariates will be evaluated. For bridging from healthy volunteer to patients, initial population PK/PD modelling and simulation will be performed using data of all 3 single-dose groups in healthy volunteer to simulate PK/PD parameters in hyperuricemia patients of single-dose with different dosage, assuming that the patient has the similar PK/PD characteristics with healthy volunteer. When patient data in 2mg dose group are available, PK/PD modelling will be optimized considering potential different PK/PD characteristics in patients in comparison to those in volunteer, and then PK/PD characteristics in patients in different dosage single-dose and multi-dose group will be simulated. Dosing in multi-dose patient study will be scheduled according to optimized simulation. At the end of study, PK/PD modelling will be further optimized using the combined data from all the volunteer and patients. Consistence of PK/PD characteristics in patients with volunteer will be evaluated, dose-exposure-response relationship and key covariates will be assessed, and afterwards the previously established modelling will be verified.

Discussion

The role of uric acid in metabolic syndrome and its pleiotropic effects in multiple organ systems has been a matter of discussion due to its complicated and outrageous connections within cellular metabolism and between signaling pathways.[5] Emerging evidence suggests a pathogenic role of hyperuricemia in the development of multiple diseases, by inducing inflammation, endothelial dysfunction, proliferation of vascular smooth muscle cells, and activation of the RAS.[6]

Hyperuricemia is characterized by excessive production and deposition of urate crystals, which is significantly associated with the development and severity of the metabolic syndrome.[6] Gout, a common metabolic disorder, is caused by chronic and/or episodic deposition of monosodium urate crystals in joints and soft tissues, prompting a gouty attack.[7] Patients with chronic refractory gout are very difficult to treat, and therapeutic options for them are limited. Pegloticase, a PEGylated recombinant mammalian uricase, was developed for the treatment of these individuals.[8,9] It is considered as "replacement therapy" for the enzyme uricase, which metabolizes urate to allantoin, making it easier for uric acid to be excreted from the body.[10] However, the major limitation of pegloticase is immunogenicity and the emergence of anti-drug antibodies that result in increased drug clearance, loss of efficacy, and infusion reactions.[11]

Our study is to evaluate the safety, tolerance and immunogenicity of the PEGylated urate oxidase for injection, a new drug produced by Xiuzheng Bio-medical Research Institute Co., Ltd, in healthy subjects and hyperuricemia patients. There are two novel aspects to this experimental design. Firstly, in order to protect the safety of the subjects, a sentinel administration design was used within each dose group. Among the 8 individuals in the group, 2 subjects were randomly assigned as sentinel subjects. The first administration observation in the queue was conducted. If no serious medical events were found within 48 hours, the observation study of other subjects in this queue was conducted. Secondly, this is a population PK model informed early-phase clinical study with seamless expansion cohort design. Using dynamic analysis and expansion cohort approach, several study objectives will be seamlessly combined and fulfilled in one single study, especially in patients with hyperuricemia, multi-dose tolerability and PK/PD study will be immediately afterwards initiated when subject blood uric acid reaches the target level in middle or high single-dose group.

Strengths and Limitations of This Study

In this study, we will use the bridge design of phase I dose-escalation, an innovative study design, which is intended to accelerate the development of new drugs and better observe the differences between healthy individuals and patients.

This is a population PK model informed early-phase clinical study with seamless expansion cohort design.

Low uric acid will not be considered as criteria for study termination, and that may bring potential risks.

Ethics and Dissemination

The trial was performed abiding by the Declaration of Helsinki[12], Good clinical practice (GCP)[13] and the guidelines of China National Medical Products Administration (NMPA). Relevant documents, including protocol, informed consent and drug inspection reports, were all approved independently by the Medical Ethics Committee of the Affiliated Hospital of Qingdao University (Ethics approval No. QYFYEC2020-042-01). All protocol violations have been reported to the Medical Ethics Committee. Written informed consent was obtained from all subjects before their participation in the study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas. All authors critically reviewed the manuscript and approved the final draft for submission. The authors would like to extend thanks to all enrolled participants and people who contributed to this study.

Funding

This study was funded by Xiuzheng Bio-medical Research Institute Co., Ltd.

Disclosure

Yaozhong Cao and Jiahui Zhang are employees of Xiuzheng Bio-medical Research Institute Co., Ltd. The authors report no other conflicts of interest in this work.

References

1. Zhu Y, Pandya BJ, Choi HK. Comorbidities of gout and hyperuricemia in the US general population: NHANES 2007–2008. *Am J Med*. 2012;125(7):679–687.e1. doi:10.1016/j.amjmed.2011.09.033
2. Edwards NL, Sundy JS, Forsythe A, Blume S, Pan F, Becker MA. Work productivity loss due to flares in patients with chronic gout refractory to conventional therapy. *J Med Econ*. 2011;14(1):10–15. doi:10.3111/13696998.2010.540874
3. Guttmann A, Krasnokutsky S, Pillinger MH, Berhanu A. Pegloticase in gout treatment - safety issues, latest evidence and clinical considerations. *Ther Adv Drug Saf*. 2017;8(12):379–388. doi:10.1177/2042098617727714
4. Tan PK, Farrar JE, Gaucher EA, Miner JN. Coevolution of URAT1 and uricase during primate evolution: implications for serum urate homeostasis and gout. *Mol Biol Evol*. 2016;33(9):2193–2200. doi:10.1093/molbev/msw116
5. Kanbay M, Jensen T, Solak Y, et al. Uric acid in metabolic syndrome: from an innocent bystander to a central player. *Eur J Intern Med*. 2016;29:3–8. doi:10.1016/j.ejim.2015.11.026

6. Yanai H, Adachi H, Hakoshima M, Katsuyama H. Molecular biological and clinical understanding of the pathophysiology and treatments of hyperuricemia and its association with metabolic syndrome, cardiovascular diseases and chronic kidney disease. *Int J Mol Sci*. 2021;22(17):9221. doi:10.3390/ijms22179221
7. Towiwat P, Chhana A, Dalbeth N. The anatomical pathology of gout: a systematic literature review. *BMC Musculoskelet Disord*. 2019;20(1):140. doi:10.1186/s12891-019-2519-y
8. Schlesinger N, Yasothan U, Kirkpatrick P. Pegloticase. *Nat Rev Drug Discov*. 2011;10(1):17–18. Erratum in: Nat Rev Drug Discov. 2011 Feb;10(2):156. doi:10.1038/nrd3349
9. Sherman MR, Saifer MGP, Perez-Ruiz F. PEG-uricase in the management of treatment-resistant gout and hyperuricemia. *Adv Drug Deliv Rev*. 2008;60(1):59–68. doi:10.1016/j.addr.2007.06.011
10. Schlesinger N, Lipsky PE. Pegloticase treatment of chronic refractory gout: update on efficacy and safety. *Semin Arthritis Rheum*. 2020;50(3S): S31–S38. doi:10.1016/j.semarthrit.2020.04.011
11. Krystexxa prescribing information; 2012. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125293s034lbl.pdf. Accessed December 22, 2023.
12. World Medical A. World medical association declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191–2194. doi:10.1001/jama.2013.281053
13. Takezawa M. Good clinical practice (GCP) in clinical trials. *Nihon Yakurigaku Zasshi*. 2011;138(5):205–208. doi:10.1254/fpj.138.205