化学药品改良型新药临床试验

技术指导原则

2020 年 12 月

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I. Introduction

Improved new drugs contain known active ingredients (Active Pharmaceutical Ingredient, API), its structure, dosage form, prescription process, delivery Drug routes, indications, etc. should be optimized and have obvious clinical advantages. and Compared with innovative drugs with completely new targets and structures, improved new drugs have more potential Identified research data on drugs with known active ingredients can shorten the clinical development cycle. With the rapid development of pharmaceutical industry technology, improved new drugs have become current new drugs One of the hot research and development directions.

Improved new chemical drugs (hereinafter referred to as improved new chemical drugs) are important Types of improved new drugs. The current "Chemical Drug Registration Classification and Application Document Requirements" "Request" clearly requires that improved new drugs should have clear clinical advantages, but currently we There are no clear technical guidelines in China that describe the clinical characteristics that improved chemical drugs should have. clinical advantages and how to demonstrate their clinical advantages through clinical trials. And our country and Some foreign regulatory agencies also have clinically relevant technical requirements for improved new chemical drugs. has a difference. In order to further clarify the clinical advantages of improved new drugs in my country and encourage This guideline is formulated to encourage the clinical development of improved new drugs in my country. chemical compound The clinical development considerations of preparations and other improved new chemical drugs are different. This guideline Combination preparations are not covered.

2. Background

Improved new drugs are marketed drugs with known active ingredients that are optimized and are Improved drug binding targets, mechanisms of action, pharmacodynamic data, and human pharmacokinetics The mechanical data, evidence of effectiveness and safety profile are relatively clear. Therefore, change

The clinical research and development of improved new drugs can draw on the clinical development experience of already marketed drugs.

Based on clear clinical needs - such as the efficacy of existing marketed drugs that need to be improved,

If the toxicity needs to be improved or the administration method needs to be optimized, optimize it. carry out necessary

clinical trials, which typically provide proof of concept for clinical benefit and ultimately

Final confirmation.

This guideline will describe the clinical advantages of new improved chemical drugs and the different

Clinical trial design and evaluation principles for improved new drugs with superior chemical drugs, in order to

Provide technical guidance and reference for clinical research and development of improved and new drugs. These guidelines apply

For improved new chemical drugs that are to be applied for marketing authorization in the country, including

Improved chemical drugs that have been marketed overseas but not marketed domestically.

This guideline only represents the current views and understanding of the drug regulatory authorities.

With the progress of scientific experiments, the relevant content in this guideline will be continuously improved and

renew. When designing and conducting research using this guidance, please also refer to

Good Clinical Practice (GCP), National

International Council for Technical Coordination of Registration of Pharmaceuticals for Human Use (International Council for

Harmonisation of Technical Requirements for Pharmaceuticals

for Human Use (ICH) and other relevant domestic published guidelines.

3. Consideration of clinical advantages

Clinical advantage is a patient's unmet clinical need. Among the target indications,

Compared with existing standard treatments, new drugs or new treatments can significantly improve the efficacy;

Or significantly reduce the adverse reactions of patients currently taking the medication without reducing the efficacy.

or risks associated with medication, or significantly improve patient medication compliance. chemical drug improvement

The clinical advantages of new drugs also follow the above principles.

The effectiveness advantages of improved chemical drugs and new drugs can be reflected in the improved

Municipal drugs, to improve effectiveness in the approved indications of domestically marketed drugs——

For example, an improved new anti-tumor drug can achieve objective relief through dosage form optimization.

The objective response rate (ORR) is significantly improved and converted into survival gains.

benefit, considered to be a clear therapeutic advantage; or the improved drug is already on the market when used in the country

Compared with the standard treatment for this indication, the indication for which the municipal drug is not approved has

Obvious clinical benefit, if there is no standard treatment for this indication, by placebo

Controlled and other trials confirm the clinical benefits of new improved chemical drugs and their clear efficacy

Advantage.

The safety advantages of new improved chemical drugs are usually the same as those of drugs already on the domestic market.

In contrast, without reducing efficacy or adding new important safety risks,

Clinically significant safety advantages have been achieved, such as an improved new antihypertensive drug.

The drug has better selectivity after structural modification, so that it can control blood pressure without lowering the

Significantly improved renal toxicity without increasing long-term cardiovascular events;

For example, a certain anti-tumor chemical drug was changed from intravenous administration to

Subcutaneous administration significantly improves the rigor of intravenous administration without reducing the efficacy.

Severe neurotoxicity.

The advantages of new and improved chemical drugs in terms of compliance refer to the new and improved drugs

Easy for patients to use. For example, for patients who require long-term subcutaneous administration,

Improvements in dosing technology have enabled human pharmacokinetics (PK)

Characteristic changes, the medication regimen was improved from one to two injections a day to one injection a week

injection, significantly improving patient compliance with medication. Adherence advantages,

There are many improvement directions that are beneficial to patients' medication, which need to be based on the purpose and basis of the topic.

At the beginning of the basically determined research and development, based on the clinical needs of patients, we worked with clinical experts and

The drug evaluation center will discuss and determine together.

4. Clinical trial design and evaluation

Improving effectiveness, improving safety or compliance are the clinical goals of improved new chemical drugs.

bed goals. According to different goals, clinical trial design and evaluation considerations should be classified and elaborated.

consider. Improved new chemical drugs may have one or more of the above advantages. During R&D and design

The experimental design should be comprehensively considered based on the main advantages.

(1) Improve effectiveness

Improving effectiveness is an important goal of improved new chemical drugs and has a clear

clinical significance. Improved new chemical drugs with the purpose of improving the effectiveness of existing drugs,

Its target indications should have clear clinical needs to improve efficacy, and it is expected to pass

Optimize the target compound structure (such as higher target selectivity and stronger inhibitory activity)

properties) and/or optimize preparation prescriptions (such as special preparations) to improve efficacy.

The clinical development of improved new drugs with the purpose of improving efficacy usually includes

Contains the following two paths:

1. The target indication is the same as that of the improved already marketed drug.

When the clinical goal of improved new chemical drugs is to improve the effectiveness of already marketed drugs

In principle, the drugs already on the market in the country should be used as a comparison to gradually prove the effectiveness.

clinical development strategy.

Before conducting clinical trials, relatively sensitive non-clinical pharmacodynamic models should be used

Obtain evidence of improved efficacy of new chemical drugs compared with existing drugs, and have the potential to increase

explanation of the mechanism of efficacy, such as improved target binding, improved efficacy, changes in

It can improve drug PK characteristics and tissue distribution to improve efficacy, or improve off-target toxicity and improve

Mechanisms such as increasing the dose in one step and improving the efficacy.

In early exploratory trials, clinical information on already marketed drugs may be considered.

Early clinical pharmacology exploration of improved new drugs. Usage of improved new chemical drugs

The dosage may be different from that of already marketed drugs. If the dosage is different, the dosage should be used in the early stage.

During the exploration, focus on usage and dosage, and explore usage and dosage that have therapeutic advantages.

Considering possible uncertainties in historical comparisons, it is recommended to use small samples and

Controlled-design trials of marketed drugs explore their efficacy advantages.

For example, early studies have shown that improved chemical drugs have significant effectiveness advantages.

It can be considered to carry out randomization and

Phase III confirmatory trials with positive controls and superior efficacy designs for drugs already on the domestic market,

to confirm the improvement in efficacy. It is necessary to comprehensively select the appropriate clinical advantages and risk-benefit ratio.

Statistical analysis methods generally do not accept equivalent or different methods unless there are sufficient reasons.

Poor design.

2. The target indication is different from that of the improved marketed drug.

Some improved new drugs may have the potential to explore new indications. Rutong

Developing new indications by optimizing the structure, dosage form or changing the administration method can

Drawing on clinical trial data of already marketed drugs, known toxicity to the structure or target

Carry out risk control, appropriately simplify early dose discovery trials, and explore new suitable

When carrying out proof-of-concept trials for appropriate diseases, the general rules for innovative drug research and development should be followed.

Progress incrementally to demonstrate benefits.

(2) Improve safety

Improving the safety of already marketed drugs is an important clinical benefit for improved new chemical drugs.

One of the benefits is that it does not reduce the efficacy or increase new important safety risks.

significantly improved clinically important safety risks and ultimately improved

Benefit-risk ratio of existing treatments.

Improved new chemical drugs aimed at improving the safety of existing drugs should first

Clarify the drug-related mechanism of adverse reactions that need to be improved - whether it is related to the activity of the chemical drug

The off-target toxicity of the component monomers or certain toxic metabolites is related to the composition of the original preparation.

Is tissue distribution related to pharmacokinetic characteristics, or is it related to a certain excipient in the prescription?

And the relevant mechanisms are studied in non-clinical research, and the safety is studied in clinical trials.

Proof of concept based on comprehensive advantages. Improved new chemical drugs aimed at improving safety

For drugs, confirmatory trials are usually required to confirm that there is no reduction in effectiveness

Under this circumstance, improved new chemical drugs have significantly reduced important safety risks.

The clinical development of improved new drugs with the purpose of improving safety usually includes

Contains the following two paths:

1. Optimize API structures with clear adverse reactions

When optimizing the structure of APIs with clear adverse reactions, the chemicals should be

The API structure should be optimized within the scope of improved new drugs in the classification and should not be changed.

Change its pharmacological and medicinal properties for disease treatment. Typically, for the API structure

Optimized improved new drugs must be developed step by step according to the research and development ideas of innovative drugs.

Conduct clinical trials, and finally confirm through confirmatory tests that the improved new chemical drugs have

Under the premise of low effectiveness, the important risks of drugs to be improved are reduced.

In the exploratory trial of improved new drugs with optimized API structure, it should be analyzed

Pharmacodynamic indicators or metabolites related to adverse reactions to be improved, such as a certain treatment

Therapeutic small molecule multi-target kinase inhibitor, through structural optimization, improved its effect on pancreatic

insulin-like growth factor receptor-1,

The binding activity of IGF-1R) to reduce the adverse effects of elevated blood sugar should be analysed.

Improve the binding activity of new drugs to IGF-1R and treat blood sugar as an important safety factor.

Safety evaluation index; for example, a certain improved new chemical drug is expected to remove

When removing a toxic metabolite, focus on the metabolite in the PK analysis - change

Whether the target toxic metabolites are removed by the structure, and whether unintended metabolites are added?

substances, whether new metabolites are toxic, etc. While focusing on target security,

It is also necessary to consider whether new unacceptable adverse reactions have been added to the surrogate endpoint

whether the efficacy is reduced, etc.

It is recommended that confirmatory trials be considered based on the effectiveness results of early exploratory trials.

The overall design of the trial is recommended to be randomized, double-blind, equivalent/non-inferior, and similar to those already on the market.

A phase III confirmatory trial with a modified drug control design. The primary endpoint should be the ability to respond to

The current gold standard of treatment clinical benefit in the target indication, or a clear clinical benefit

It is a surrogate endpoint for predicting clinical benefit and has strict statistical assumptions. should be in

On the premise that the conclusion of effectiveness equivalence/non-inferiority is established, the target safety to be improved

Achieve clinically meaningful improvements in events. If you optimize the API structure and improve

It is possible to achieve superior efficiency while being safe, and it is recommended to adopt superior efficiency design. according to goals

The safety advantages of existing treatments and modifications for indications may lead to acceptable effectiveness of

Non-inferior research design.

2. Improvement methods other than API structure

Some improved new chemical drugs can be improved through optimization methods other than API structure.

Safety, such as optimizing the prescription process, changing dosage forms or usage, etc. this situation

It is more complex and clinical trial design must be considered based on different situations.

For example, optimizing the dosage form or administration method, by changing the pharmacokinetic characteristics of API

To achieve the goal of improving safety and tissue distribution, PK comparisons are usually required.

For the test, evaluate whether the PK characteristics of the improved new chemical drug meet expectations; then

Randomized controlled clinical trials will be conducted to confirm whether the improvement of PK has clinical benefit.

The principles of consideration in the design and evaluation of confirmatory clinical trials are clearly related to those of optimization.

API structure of adverse reactions.

In some cases, by replacing or removing an excipient with a clear adverse reaction

means to directly improve safety, such as through prescription optimization to

In addition to ethanol, there is a clear benefit for patients who are allergic to ethanol and require treatment with this product.

clinical significance. This optimization does not change the pharmacokinetics and safety and efficacy characteristics of the API.

In this case, the applicant can communicate with the Center for Drug Evaluation to discuss whether

Exemption from clinical trials using non-clinical research data.

(3) Improve compliance

Without affecting the safety and effectiveness of chemical drugs, improve patient performance through improvements

Medication compliance and convenience are also a common type of improved new drugs.

More common situations include: (1) Changing the route of administration, such as changing intravenous injections to

Other dosage forms to facilitate patient administration and/or to increase local drug concentration; (2)

The ordinary dosage form is changed to a sustained-release and long-acting preparation to extend the dosing interval, which is convenient for patients.

Medication can also avoid fluctuations in clinical indicators caused by patients missing medications; (3)

Special formulations developed for specific patient populations.

If the PK behavior of the improved new drug changes compared with the original drug, it is necessary to first

First, conduct PK studies to explore reasonable doses and dosing intervals to meet the preset

Clinical drug requirements, and then conduct randomized controlled clinical trials to verify drug improvements

New drugs must at least remain as effective and safe as the modified drugs.

Improve patient medication compliance.

To avoid medication difficulties for specific patients (dysphagia, avoidance of medication), etc.

Improved new chemical drugs with special preparations, targeting people with specific diseases.

For special patients, such as special dosage forms for infants and young children, the clinical benefits are clear and can

Before designing an improved new formulation, communicate with the Drug Evaluation Center and determine

levy and develop specific clinical development requirements.

(4) Others

Some improved new chemical drugs may have other advantages, such as psychotropic drugs

Product development, special prescription processes to prevent drug abuse, etc. For unfinished matters, it is recommended to contact

The Center for Drug Evaluation communicates the overall ideas and specific clinical trials related to clinical research and development

Key elements of design.

5. Summary

The development of new improved chemical drugs is usually based on already marketed active ingredients.

There are clear clinical needs and improvement directions. Compared with innovative drugs, their research and development

The cost is low, the success rate is high, and it has important social significance. Applicants are encouraged to refer to this

The clinical development path provided by the technical guiding principles ensures reasonable and orderly research and development. right

Clinical advantages and trials of improved new chemical drugs not covered by this guideline

considering experimental design and other considerations, applicants are encouraged to communicate with the Center for Drug Evaluation to discuss

At the same time, we will promote the clinical research and development of improved chemical drugs and new drugs.