

Unique Protocol Identification Number: Gadolinium 1.0

**Safety Evaluation of Linear and
Macrocyclic Gadolinium-Based Contrast
Agents for Patients with Mild to Moderate
Renal Insufficiency Undergoing Enhanced
Magnetic Resonance Imaging
(Interventional Prospective Study)
Clinical Trial Protocol**

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Protocol Summary

Study Title	Safety Evaluation of Linear and Macroyclic Gadolinium-Based Contrast Agents for Patients with Mild to Moderate Renal Insufficiency Undergoing Enhanced Magnetic Resonance Imaging	
Study Unit	Lishui Central Hospital	
Study Type	Interventional	
Time Perspective	Prospective	
Study Drug	Gadodiamide Injection (OMNISCAN™), Gadoteric Acid Meglumine Salt Injection (Jia Di Xian™)	
Study Description	<p>Brief Summary:</p> <p>The purpose of this study is to evaluate the safety of linear and macrocyclic gadolinium-based contrast agents for patients with mild to moderate renal insufficiency. The study will compare the incidence of adverse events of gadodiamide and gadoteric Acid Meglumine Salt for patients with mild to moderate renal insufficiency undergoing enhanced magnetic resonance imaging.</p>	
Group/Cohort	Gadodiamide: Patients who have undergone contrast-enhanced MRI using Gadodiamide contrast agent for clinical purposes.	Drug: Gadodiamide Injection (OMNISCAN™)
	Gadoteric Acid Meglumine Salt: Patients who have undergone contrast-enhanced MRI using Gadoteric Acid Meglumine Salt contrast agent for clinical purposes.	Drug: Gadoteric Acid Meglumine Salt Injection (Jia Di Xian™)
Eligibility Criteria	<p>Inclusion Criteria:</p> <ol style="list-style-type: none"> 1. Patients aged 18 to 80 years old who require gadolinium-based CE-MRI; 2. Patients with renal function $30\text{ml/min}/1.73\text{m}^2 \leq \text{eGFR} < 90\text{ml/min}/1.73\text{m}^2$; 3. Patients who are able and willing to comply with the required inspection requirements. <p>Exclusion Criteria:</p> <ol style="list-style-type: none"> 1. Patient who experienced allergic reactions to previous gadolinium based contrast agents; 	

	<ol style="list-style-type: none"> 2. Patient who had used gadolinium based contrast agents within 3 months; 3. Patient with acute renal failure; 4. Patient who cannot comply with or cannot tolerate the necessary fluid replenishment procedures; 5. Patient with major mental illness, impaired consciousness or other diseases considered by researchers to affect observation.
Outcome Measure	<p>Primary Outcome indicators: Record the incidence of various adverse events;</p> <p>Secondary outcome indicators:</p> <ol style="list-style-type: none"> 1. Changes of serum creatinine and inflammatory factors (TNF-α, hs-CRP, IL-6) before and after CE-MRI 2. Patient skin examination and evaluation: evaluation of relevant indicators of skin biopsy (proliferation of fibroblasts in subcutaneous tissue, thickening of collagen fiber bundles)
Enrollment	600 participants

I. Sponsor Information

(I) Name of sponsor

Jiansong, Ji

(II) Address of sponsor

Lishui Central Hospital, No.289 Kuocang Road, Lishui City, Zhejiang Province

(III) Contact information of sponsor

0578-2285018

(IV) Relevant qualification documents of sponsor

The relevant qualification documents of the sponsor will be provided in a separate letter.

II. Purpose and contents of clinical trial

(I) Purpose

To compare the incidence of adverse events of linear and macrocyclic gadolinium-based contrast agents for patients with mild to moderate renal insufficiency undergoing enhanced magnetic resonance imaging.

(II) Contents

This trial is a prospective, interventional study. According to the requirements of the study, 600 cases of patients with mild to moderate renal insufficiency were enrolled. Gadodiamide and gadoteric acid meglumine salt were used for enhanced MRI. Observe the adverse reactions within 60 minutes of using the gadolinium contrast agents; follow up by telephone at 3, 6, 12, and 24 months after the inspection.

III. Background information of clinical trials

The principle of Magnetic Resonance Imaging (MRI) relies on the magnetic field generated by water molecules in the human body. It has high resolution in soft tissues (such as the nervous system, parenchymal organs, and muscle tissue), and uses non-ionizing electromagnetic radiation. Known exposure risk, many imaging parameters (sequence, proton density, T1 and T2 relaxation time) and many other advantages, since it entered the clinic in the 1980s, it has been clinically proven to be a valuable imaging diagnostic method. In the early clinical practice, MRI was mainly used for unenhanced magnetic resonance imaging, and the value of Contrast Enhanced-Magnetic Resonance Imaging (CE-MRI) in the diagnosis of diseases was not recognized. In the later stage, due to CE-MRI in small lesions, inflammation, edema and tumor Such diagnostic advantages have become an important supplement to MRI. At least about 30% of disease MRI diagnosis requires injection of magnetic resonance contrast agents.

In 2000, Cowper described the mucoedema-like sclerosis skin disease of renal dialysis patients in the Lancet magazine, that is, Nephrogenic Systemic Fibrosis (NSF). In 2006, Grobner

reported nephrogenic skin. The predisposing factor of disease or NSF may be gadolinium ion. In the same year, Marckmann discovered that NSF may be caused by the use of gadolinium diamine during MR examination. Due to the serious harm of NSF, foreign scholars began to pay explosive attention to the relationship between gadolinium contrast agent and NSF, and aroused clinical concern about the safety of gadolinium contrast agent. Subsequently, the European Society of Urology and Radiology (ESUR) classified gadolinium contrast agent as high-risk, medium-risk and low-risk , And use gadolinium contrast agent according to the classification of renal function. Since then, new reports of NSF have gradually decreased. Due to the long-term concern about the safety of gadolinium contrast agent, Dr. Tomonori Kanda published an article in the Journal of Radiology in Hyogo Cancer in 2014 and explained for the first time the relationship between T1 hyperintensity and gadolinium deposition in the brain dentate nucleus and globus pallidus. In 2015, Dr. Robert J. McDonald and Kanda of the Mayo Medical Center in the United States published an article in the Journal of Radiology at the same time and confirmed the presence of gadolinium deposits in the brain through an autopsy. Later, foreign scholars paid great attention to the phenomenon of gadolinium contrast agent and gadolinium deposition in the brain. Some scholars believe that the brain gadolinium deposition (dentate nucleus hyperintensity) is caused by linear contrast agent rather than a large ring, but some scholars believe that a large ring may also be It causes gadolinium deposition in the brain. After reviewing numerous evidences, in order to avoid potential harm, the European Medicines Agency (EMA) finally decided in July 2017 to restrict the application of some linear gadolinium contrast agents to humans.

Current research shows that the occurrence of NSF diseases is related to patients with renal insufficiency, especially in patients with severe renal insufficiency with $eGFR < 30 \text{ ml/min/1.73m}^2$. During 1997-2007, there have been more than 500 cases of NSF related reports. In 2006, the US FDA issued a public health advisory (PHA) to alert the public to the occurrence of NSF. In the following year, the labels of all gadolinium-containing contrast media and drugs must state several conditions that may cause the risk of NSF: (1) Acute or chronic severe renal insufficiency, that is, the glomerular filtration rate is less than $30 \text{ ml/(min} \cdot 1.73 \text{ m}^2\text{)}$; (2) Severe acute renal insufficiency caused by hepatorenal syndrome or during the perioperative period of liver transplantation.

Due to nephrogenic systemic fibrosis (NSF) and Gadolinium deposition disease (Gadolinium

deposition disease, GDD) harm or potential harm to the human body, the FDA banned some linear GBCAs (such as: gadolinium diamine, gadolinium meglumine) in July 2015) Is used for special populations (eGFR<30ml/min/1.73m², acute kidney injury), while the European Medicines Agency (EMA) banned some linear GBCA intravenous (such as: gadolinium diamine, Gadopentetate meglumine) is used for body enhancement. Because the stability of large ring GBCA is better than linear GBCA, FDA and EMA do not make special requirements. Gd-terol, gadobutrol and meglumine gadoterate are all macrocyclic GBCA. Gd-DOTA is the only ionic macrocyclic gadolinium contrast agent with the best stability (conditional stability constant, dissociation half-life and chelation Evaluation of parameters such as residues), the safety is better. At present, the GBCA approved by the China Food and Drug Administration (CFDA) includes gadopentetate meglumine, gadolinium diamine, gadolinium fuseamide, gadolinium benzamide, gadolinium disodium gadolinate, and gadolinium. Butrol, gadoterol and gadoterate meglumine. In this study, linear gadolinium and macrocyclic gadolinium were used in enhanced magnetic resonance examinations. Acute adverse reactions (1h) and delayed adverse reactions (1h-1W) in patients with mild to moderate renal insufficiency after contrast injection , The occurrence of late-onset adverse reactions (1W-3M). To explore the incidence of adverse reactions of linear gadolinium contrast agents represented by gadolinium bisamine and macrocyclic gadolinium contrast agents represented by gadolinium meglumine in patients with mild to moderate renal insufficiency. For patients with mild to moderate renal insufficiency when doing CE-MRI, make the best choice of gadolinium to reduce the incidence of adverse reactions in such patients during enhanced MRI.

IV. The characteristics and safety of the drug

(I) Characteristics of the drug

Generic name: Gadodiamide Injection

Product name: OMNISCAN

Sample specifications: 15ml: 4.305g (a sterile solution containing 287mg/ml gadodiamide)

Generic name: Gadoteric Acid Meglumine Salt Injection

Commodity name: Jia Di Xian

Sample specifications: 15ml: 5.654g (a sterile solution containing 377mg/ml gadoteric acid meglumine salt)

After intravenous injection of gadolinium contrast agent, it is mainly distributed in the extracellular fluid of the body, does not bind to serum albumin, does not pass through the healthy blood-brain barrier, is filtered by the glomerulus, and is excreted as a prototype; when the kidney function is normal, The plasma half-life is about 90 minutes, and the plasma clearance rate of patients with renal insufficiency will be slower.

(II) Safety data of clinical application so far

In 2016, Eric de Kerviler and others reviewed the 25-year clinical use of gadoterate meglumine (DOTAREM) and the safety data of phase I-IV clinical trials. In the safety data of phase I-IV Gadoterate meglumine clinical trials, 2822 patients, 241 (8.5%) patients, 405 adverse events occurred, 113 cases (4.0%) may be related to gadoterate meglumine. There were 27 serious adverse events (1.0%), including 2 cases (0.07%) related to gadoterate meglumine. No new adverse reactions were found in the post-marketing safety study, with adverse events <1.0%. During 25 years, 50 million injections, only 3797 patients had 8397 adverse reactions, the incidence of adverse reactions was extremely low (0.007%). Gadolinium diamine was approved for MRI diagnosis of adult central nervous system diseases in 1993. It is a non-ionic MR contrast agent. Like other paramagnetic contrast agents, it can shorten tissue relaxation time (T1 and T2, Mainly T1). The enhancement effect depends on the blood supply of the tissue. The contrast agent can be distributed in the blood vessel and extracellular space, and the enhancement effect is obvious. A Meta-analysis of 214,342 patients who used gadolinium-containing contrast agents included 42 documents. The incidence of all adverse reactions was 0.19% (397/214342), and the incidence of adverse reactions with gadolinium diamine was 2.52% (10/397).). Gadolinium diamine is the first reported NSF-related gadolinium-containing contrast agent, and its ligand is a non-ionic linear chelate. In risky subjects, 3%-18% of the contrast agent will have NSF.

V. Indications, contraindications and precautions of drugs

【Indications】

This product is only used for disease diagnosis.

MRI examination for the following diseases:

1. Brain and spinal cord disease
2. Spinal disease
3. Other systemic pathological examinations (including angiography)

【Contraindications】

1. People who are allergic to the components of this product should not be used. Patients with a history of allergic reactions or suspected allergic reactions to other gadolinium chelates should not use this product.
2. Contraindications related to magnetic resonance: patients with built-in pacemakers and patients with built-in vascular clips.

【Precautions】

This product is for intravenous injection only. If there is extravascular exudation, it may cause local intolerance reaction, then local treatment should be done.

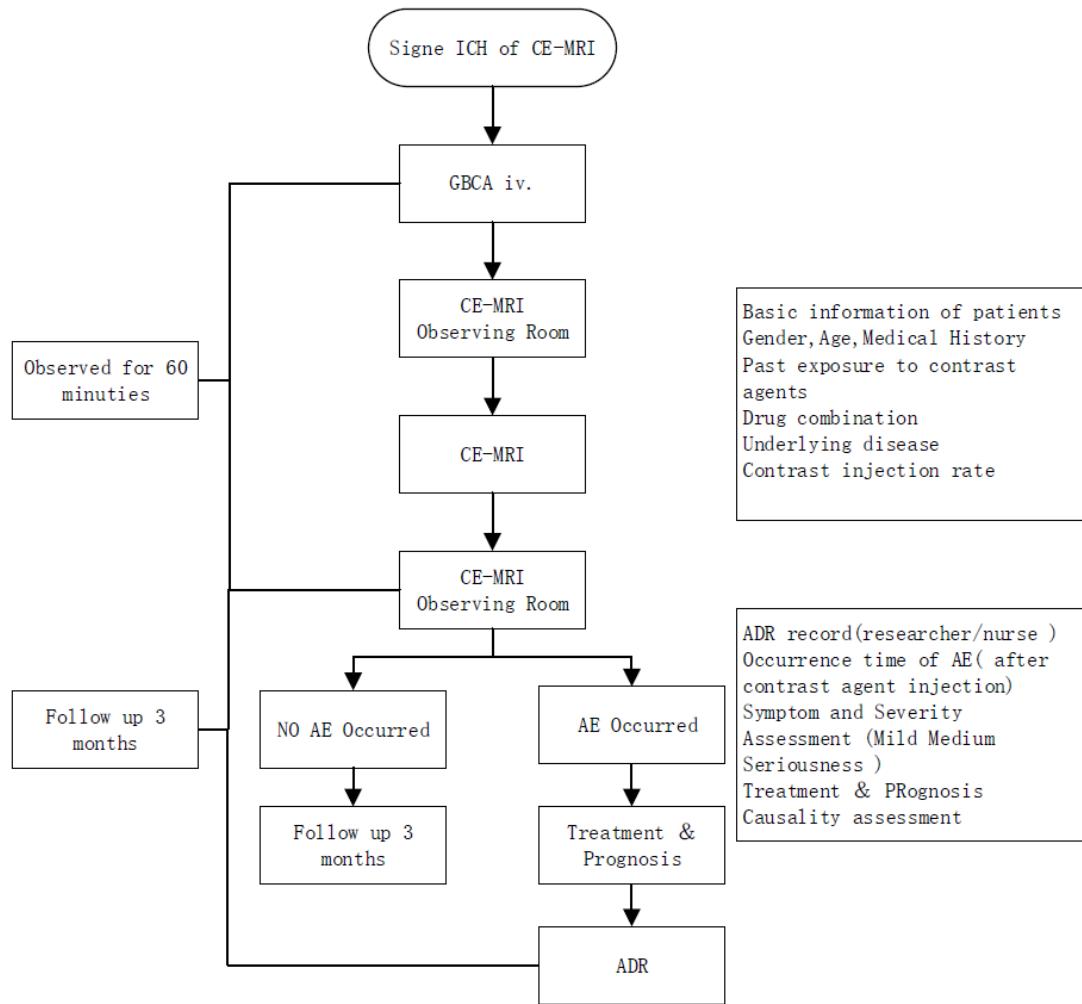
This product is forbidden to be used for subarachnoid (or epidural) injection.

Routine preventive measures should be taken in the following situations: such as screening out patients with pacemakers, built-in vascular clamps, infusion pumps, neurostimulators, electronic cochleae, and patients with suspicious metal foreign bodies in their bodies, especially in the eyes.

VI. Overall design

(I) Design of the trial

This trial is a post-marketing, single-center, prospective, and safety interventional study. The trial process is as follows:



(II) Patient selection and withdrawal

1. Inclusion Criteria

- 1) Patients aged 18 to 80 years old who require gadolinium based CE-MRI;
- 2) Patients with renal function $30\text{ml/min}/1.73\text{m}^2 \leq \text{eGFR} < 90/\text{min}/1.73\text{m}^2$;
- 3) Patients who are able and willing to comply with the required inspection requirements.

2. Exclusion Criteria

- 1) Patient who experienced allergic reactions to previous gadolinium based contrast agents;
- 2) Patient who had used gadolinium based contrast agents within 3 months;
- 3) Patient with acute renal failure;
- 4) Patient who cannot comply with or cannot tolerate the necessary fluid replenishment procedures;
- 5) Patient with major mental illness, impaired consciousness or other diseases considered by

researchers to affect observation.

3. Early withdrawal and termination of patients

- 1) Any situation that the researcher thinks the patient needs to quit;
- 2) Any situation that the patient's guardian thinks it is necessary to withdraw from the CE-MRI.
- 3) After the patient withdraws, the relevant information is no longer tracked and recorded, but the reason for the withdrawal should be recorded in detail.

(III) Visit description

Visit 1: after signing the informed consent form for CE-MRI;

Visit 2: within 60 minutes after contrast injection;

Visit 3: within 3 months after contrast injection;

Visit 4: within 6 months after contrast injection;

Visit 5: within 12 months after contrast injection;

Visit 6: within 24 months after contrast injection;

Visit content: study-CRF table-patient basic information table

Visit 1: study-CRF table-patient basic information table

1. Name of hospital:
2. Registration Date:
3. Contact details of the patient/its agent:
4. source: Outpatient () Hospitalized ();
5. Clinical department;
6. Name:
7. Sex: Male () Female ();
8. Age:
9. Weight: Kg;
10. Height: CM;
11. CE-MRI informed: yes () no ();
12. CE-MRI Indications:

13. Gadolinium contrast injection time:

14. Gadolinium contrast agent injection volume: ml;

15. Gadolinium contrast injection method: Push () Machine injection () (Please mark the injection speed);

16. Previous image enhancement examination history: time; Contrast agent name; Yes/No adverse events occurred;

a) yes time symptom severity;

17. Past history of adverse drug reactions: yes/no, yes time、AE symptom、severity;

18. The latest serological examination before CE-MRI and the serological examination within 2 weeks after CE-MRI;

19. History of allergy: yes/no, yes, allergy description;

20. Suspected existing disease:

21. Existing disease treatment plan: medical treatment () oral () Intramuscular injection () Intravenous injection () Surgical treatment () surgical intervention () Else;

22. History of illness:

a) Disease name Date of diagnosis duration;

23. Daily medication (Take medication within 1 week):

a) Generic name of the drug Taking method dose

24. Other information

25. Adverse event: yes () no ()

Visit 2, Visit 3, Visit 4, Visit 5 and Visit 6 Study-CRF Form-Contrast Adverse Events

1. Name:
2. Sex:
3. Age:
4. Weight:
5. Time to onset of adverse events:
6. Severity assessment:
7. Suspected drugs: Generic name (including dosage form)、Manufacturer、Production batch、Dosage、Start and end time of medication、Reason for medication;

8. Concomitant drugs: Generic name (including dosage form)、Manufacturer、Production batch、
Dosage、Start and end time of medication、Reason for medication

Concomitant drugs are those used within 24 hours;

9. Other suspected factors: Such as: patient disease progression, patient treatment plan, etc.;

10. Adverse events affect organ systems:

11. Adverse event name: refer to MedADR glossary;

12. Process description and handling of adverse events (attachment available);

13. Adverse event results:

Recover () Improve () Not getting better () Unclear ()

Have adverse events () manifestation: _____

death () Direct cause of death: _____ Time of death: y m d

14. Impact on the original disease:

Not obvious () Prolonged course () Worsening () Cause adverse events () Cause death ()

15. Whether the withdrawal/reduction reaction is reduced or disappeared:

yes () no () unclear () No discontinuation or dose reduction ()

Whether the same reaction occurs again after re-use

yes () no () unclear () Unused ()

16. Relevance evaluation:

Certain () Very likely () Possible () May be irrelevant ()

Wait to be evaluated () Can't evaluate ()

17. Reporter's information: name, contact number, email address, occupation

(IV) Evaluation Standard

1. Adverse events

Adverse Event (AE) : Adverse clinical events that occur during the course of drug treatment may not necessarily have a causal relationship with the drug.

Serious Adverse Event (Serious Adverse Event, SAE): the reaction of one of the following

damages caused by the use of drugs:

- 1) Cause death;
- 2) Life threatening;
- 3) Carcinogenic, teratogenic, and birth defects;
- 4) Cause significant or permanent human disability or damage to organ function;
- 5) Lead to hospitalization or prolonged hospital stay;
- 6) Causes other important medical events, if not treated, the conditions listed above may occur.

Report serious adverse events:

- 1) When an aggregated, serious, or new (not listed in the ACR Contrast Media Guide) adverse reaction occurs, the investigator must within 24 hours of being notified:
- 2) Fill in the "Adverse Event/Reaction Report Form" and report to the Research Center Ethics Committee;
- 3) Entering adverse reaction events into EDC allows researchers to process relevant safety information/take corresponding measures immediately;
- 4) When a known mild to moderate adverse reaction occurs, the researcher needs to fill in the "Adverse Event/Reaction Report Form" within 15 days after being notified, and complete the entry of the adverse reaction event into the EDC to facilitate timely information about the adverse event;

2. Severity assessment

AE severity refers to the degree of occurrence of a specific event (which can be SAE or ordinary AE), but the event itself may have relatively small medical significance.

Principle of severity

Mild symptoms or signs that are easily tolerated

Moderate symptoms and signs cause discomfort and affect daily life;

Severe Cannot engage in daily life or work, need sick leave or necessary treatment.

3. Causality assessment

The causal relationship between adverse events and drugs is often based on the investigator's clinical judgment and understanding of the trial drug, but generally can be comprehensively analyzed from the following aspects:

The time relationship between medication and adverse events and whether there is a

dose-effect relationship;

Whether it is a known type of drug reaction;

Whether the adverse events alleviate or disappear after stopping or reducing the dose;

Under strict and safe conditions, when the test is repeated, whether the adverse event recurs;

Whether adverse events can be explained by the effects of concomitant medications, the patient's disease progression, and the effects of other treatments;

The causal relationship between adverse events and drugs can be judged according to the WHO Uppsala ADR Testing Center Guidelines. The six-level evaluation standard is affirmative, very likely, possible, unlikely, unassessed, unable to assess.

VII. Trial quality control

The quality of clinical trials refers to its scientificity, reliability, accuracy and completeness.

Quality assurance is an important cornerstone of whether the trial can be successful. As a quality management standard, GCP is its tenet and goal to ensure quality. GCP's methods and measures to ensure the quality of clinical trials mainly include the following:

To specify the qualifications and responsibilities of all relevant personnel in clinical trials;

To stipulate the conditions, procedures and contents of the trial plan for conducting clinical trials;

Specify test records, reports, data processing and archiving systems;

To stipulate management systems for the preparation, distribution, use, and recovery of experimental drugs;

Develop and follow standard operating specifications (SOP) to regulate various tests and operations;

Establish a multi-step quality assurance system;

Contains 4 links: quality control, supervision, inspection and inspection.

(I) Quality Control

PI is fully responsible for quality control, and each researcher or other participating personnel

implements and executes it.

1. Qualifications and responsibilities of test personnel

The investigator is a key factor for the success of clinical trials. Whether it can be completed smoothly and with high quality depends mainly on the investigator. Combined with ICH-GCP, foreign scholars have summarized 12 gold standards for qualified researchers, as follows:

Familiar with and follow the test plan, read, agree, follow, reach and archive;

Select and train suitable researchers, training, personnel list, resume, and knowing;

Observe and record the test data carefully;

Ensure that the research equipment is adequate and reliable;

Maximum protection of patients;

Accurately predict and record the selection of patients;

Strictly count and manage test drugs;

Record and report adverse events in a timely manner;

Ensure the quality of laboratory evaluation;

Standardize the preservation of test data and files;

Maximize data quality;

Communicate information comprehensively and effectively

This test is a single-center study, and the personnel involved in the test are as follows:

The principal investigator (PI) is the chief researcher;

Sub-investigator (Sub-investigator, SI) participants such as nurses, technicians, etc.;

PI combines the test situation and the center's situation, and arranges qualified personnel to perform related functions.

2. Test plan and implementation of SOP quality assurance

After the trial program is completed, the participating researchers will discuss and revise the program;

After the revised draft is completed, it will be reviewed by the clinical trial committee;

Revise according to the comments of the clinical trial committee to determine the trial plan;

Finalize the test plan and invite statistics and data management personnel to determine;

According to the confirmed test plan, the research database was developed.

(II) Monitor

The purpose of the audit is to protect the rights and interests of patients, the test records and report data are accurate, complete and consistent with the original data, and to ensure compliance with the test plan, standard operating procedures, GCP and current relevant laws and regulations;

The inspector who performs the inspection shall be appointed by the sponsor.

VIII. Patient protection

The Declaration of Helsinki and GCP are important documents to protect the dignity, health, safety and legal rights of patients; this trial follows the Declaration of Helsinki and relevant Chinese clinical trial research norms and regulations for clinical trials. The ethics committee and informed consent are the main organizations and measures to protect the rights and interests of patients. Before the start of the clinical trial, the trial protocol needs to be reviewed and approved by the ethics committee and signed an approval opinion before implementation. During the clinical trial, any modification of the trial protocol should be approved by the ethics committee before being implemented.

Clinical investigators must explain to patients that participation in clinical trials is voluntary, and that they have the right to withdraw from the trial at any stage of the trial without discrimination or retaliation, their medical treatment and rights will not be affected, and they can continue to receive other treatments Or treatment. Patients must be made aware that their participation in the trial and their personal data during the trial are confidential. It is also necessary to inform patients of the nature, purpose, expected benefits, possible risks and inconveniences of the clinical trial, and inform patients that the trial complies with the rights and obligations of patients specified in the Declaration of Helsinki, so that patients have sufficient time to consider whether they are willing to participate in clinical trials.

IX. Data management and statistical analysis

A standardized data management plan helps to obtain true, accurate, complete and reliable

high-quality data; a detailed statistical analysis plan helps to ensure that the statistical analysis conclusions are correct and convincing.

(I) Data management

Clinical data management includes collection and data management system establishment, case report form and database design, data acceptance and entry, data verification and questioning, medical coding, external data management, blind review, database locking, database unlocking and relocking, export and transmission, data and data management document filing;

This experiment uses an electronic CRF form for manual review and computer inspection; follow the guidelines for filling in the CRF for this test; if there is questionable data after manual review or computer inspection, a data questioning form will be sent to the clinical trial unit and the investigator will sign and confirm the value Correction, data questioning and correction form should be kept.

(II) Statistical Analysis

1. Statistical Analysis Plan

The statistical analysis plan is led by the statistician, assisted by the data administrator, sponsor and researcher, and formulated through consultation. After the trial plan is finalized, statisticians are selected; when about 50% of the enrollment is completed, the statistical analysis plan is started, and the statistical analysis plan is determined when the enrollment of the last case is completed; the statistical analysis plan can be performed before the database is finally locked modify.

2. Sample size

This study is a post-marketing safety observation study, with a design sample size of 600 cases.

3. Statistical analysis sets and statistical methods

Because this trial is a safety monitoring study, the analysis set includes all patients who have used the study drug and have undergone safety evaluation.

The statistical analysis was done using SAS 9.4. This study does not estimate missing data.

All statistical tests are at the 5% level of significance, and the two-sided test may be expressed with a 95% confidence interval.

Describe the basic information of the patient, and use the mean, median, standard deviation, and range for continuous variables for statistical description. Categorical variables (nominal variables/ordinal variables) are described by frequency and frequency.

Calculate the number of adverse events, serious adverse events, adverse reactions and serious adverse reactions, the incidence and its 95% confidence interval, and the 95% confidence interval is calculated using the exact probability method. They are described separately according to the severity of adverse events and whether they are related to drugs.

Taking adverse reactions and adverse events as dependent variables, taking gender, age, concomitant diseases, gadolinium diamine, gadoteric acid meglumine exposure, combined medication and other factors as independent variables, using Logistic regression to analyze the occurrence of adverse reactions or adverse events. Significant influencing factors, and estimate the odds ratio and its 95% confidence interval. The variables entered into the model will be confirmed in the statistical plan before the data is locked.

X. Trial summary and results publication

After the drug clinical trial summary is completed, at least there should be a statistical analysis report and a clinical trial summary report; after consultation with the investigator, the trial protocol or the results of the analysis after the analysis can be published, and the disclosure of confidential data is strictly prohibited.

The statistical analysis report is completed within one month after the database is locked, and the clinical trial summary report is completed within one month after the statistical analysis report is completed.