Supplementary file 1

Ethics Committee Approval of Fujian Provincial Hospital

Approval number: K2021-12-022

Study Tile	Remimazolam for the prevention of emergence delirium in children following tonsillectomy and adenoidectomy
Department	Anesthesiology
Principal Investigator	Yusheng Yao
List of Documents	1. Study Protocol (version 1.0, Dated 10/11/2021) 2. Informed Consent Form (version 1.0, Dated 10/11/2021) 3. Proposed advertising material 4. Other
Evaluation Comments	☒ Approval ☐ Disapproval ☐ Conditional Approval ☐ Retrial after Revision ☐ Terminate or Suspend Chan Fayang Ethics Committee of Fujian Provincial Hospital Approval Date: 08/12/2021

Address: No. 134, Dongjie, Fuzhou, 350001, Fujian, China
Tel: 0591-88216023

Supplementary file 2

Informed Consent Form

Study Title: Remimazolam for the prevention of emergence delirium in children following tonsillectomy and adenoidectomy under sevoflurane anesthesia

Study Doctor: Dr. Yao Yusheng, Department of Anesthesiology

Emergency contact number: +86-0591-88217841

Sponsor/Funder(s): the Comfort Medical Research Project of Fujian Strait Medical and Health Exchange Association (No. 2020-HYH-03), the Medical Innovation Project of Fujian Province (No.2019-CXB-6), and the Natural Science Foundation of Fujian Province (No. 2021J01378).

Contact numbers and information are noted at the end of this document.

INTRODUCTION

As a Substitute Decision Maker, you are being asked to provide informed consent on behalf of a person who cannot provide consent for him/herself. If the participant gains the capacity to consent for him/herself, your consent for them will end. Throughout this form, "you" means the person you are representing.

You are invited to participate in this trial because you will undergo tonsillectomy and because you are between the ages of 3 and 7 years old. We invite you to participate in a clinical trial approved by the Ethical Committees of Fujian Provincial Hospital, “Efficacy of remimazolam on emergence delirium in pediatric patients". Sevoflurane, as an inhalation anesthetic for the induction and maintenance of general anesthesia, is the most commonly used in pediatric patients. However, emergence delirium is a well-known postoperative behavior disorder after sevoflurane anesthesia in the pediatric population, with a reported incidence of up to 67%. It has been suggested that ‘no eye contact’, ‘no purposeful action’, and ‘no awareness of surroundings’ significantly correlate with emergence delirium. Emergence delirium may cause dissatisfaction among parents and self-injury and may increase the workload of postanesthesia care unit (PACU) nurses. Given the adverse impact of emergence delirium on the recovery quality of pediatric patients and its heavy burden on society and the economy, it is imperative to find a medical measure that can effectively reduce the incidence of emergence delirium. The study explores a method to reduce the incidence of emergence delirium in pediatric patients. This consent form

provides information to help you decide whether to participate in the study. Please read this informed consent carefully and feel free to ask any questions you may have. All your questions should be answered to your satisfaction before deciding whether to participate in the study.

HOW MANY CHILDREN WILL TAKE PART IN THIS STUDY?

This study will be conducted in Fujian Provincial Hospital. The study will recruit 104 pediatric patients, and we estimate that it will take half of one year to complete. We hope that this study's results will positively impact the recovery quality of pediatric patients undergoing tonsillectomy and adenoidectomy.

WHAT IS THE BACKGROUND INFORMATION FOR THIS STUDY?

Remimazolam is a brand-new general anesthetic that is an ultrashort-acting benzodiazepine metabolized by tissue esterases to an inactive compound. Given that it is rapidly hydrolyzed to an inactive metabolite, it is not affected by hepatic or renal impairment. In addition, remimazolam has a predictable duration and controlled sedation. To date, remimazolam has shown promising results in adults, and further trials directed at the pediatric population are warranted and undergoing. Remimazolam is increasingly being used for procedural sedation and general anesthesia in children. This drug is prescribed off-label for this indication and is widely believed to be beneficial, as many medicines in pediatrics are. There is a well-known knowledge gap regarding the efficacy and safety of medicines in pediatric patients, and 70% of prescribed medications are estimated to be off-label, laying children open to a high risk of adverse effects. Therefore, it is necessary to explore the effect of remimazolam on emergence delirium in children after sevoflurane anesthesia and long-term negative behavioral changes after discharge. This study may help overcome challenges related to gaining access to this treatment and support safe and effective off-label use of remimazolam in children with emergence delirium. **We attempted to investigate whether a single intravenous injection of remimazolam at the end of surgery could reduce the incidence of emergence delirium in children.**

WHAT IS THE PURPOSE OF THIS STUDY?

This study aimed to identify the effectiveness of remimazolam at the end of tonsillectomy and adenoidectomy for preventing emergence delirium in children under sevoflurane anesthesia. Clarifying the impact of a single bolus of intravenous remimazolam on emergence delirium and

other negative behavioral changes in pediatric patients undergoing tonsillectomy and adenoidectomy surgery can provide innovative ideas and references for improving the recovery quality and postoperative quality of life in pediatric patients.

WHAT WILL HAPPEN DURING THIS CLINICAL STUDY?

The entire study may last from 3 days involving a phone call.

The study develops in steps:

1. Screening assessments to check that you can be included in the study
2. A single dose of study drug at the end of surgery
3. A follow-up survey to identify any abnormal behaviors 3 days postoperatively

A more detailed description is given in the following sections:

If you are willing to participate in this study, you will be assigned at random to one of two groups: the remimazolam group and the saline group. Suppose you are randomly allocated to the remimazolam group. In that case, you will receive an intravenous injection of 0.2 mg/kg remimazolam at the end of the procedure. If you are in the saline group, you will receive an equal volume of 0.9% saline injection at the end of surgery.

This trial is a double-blind study, which means that neither you, the study doctor, nurse, nor the research assistant will know which group you are in. However, your group assignment can be determined if knowing your group assignment becomes necessary for your safety. Additionally, requests to reveal your group assignment for your information or participation in other research studies will be considered when this study is completed and the results are known.

We primarily wondered whether intravenous remimazolam 0.2 mg/kg could reduce the incidence of emergence delirium in children. We are also interested in other aspects of recovery quality, such as the peak Pediatric Anesthesia Emergence Delirium (PAED) score, postoperative pain intensity, and postoperative behavior changes on day three.

WHAT DATA WILL BE COLLECTED FROM YOU?

At the time of enrollment, we will need to collect personal information (name, phone number, age, sex, and hospital ID number). This information is required to track side effects and allow us to communicate with you for follow-up or in case you agree to participate in future studies related to remimazolam. When you are ready to leave the operating room, we will collect

information about the peak PAED score, emergence time, postoperative pain intensity, and length of PACU stay. The researchers will follow up by phone or person three days after the surgery to screen for any negative postoperative behavioral changes based on a short survey called the Post Hospital Behavior Questionnaire. Although these are uncommon, a follow-up survey will help us identify any abnormal behaviors that may be related to sedation, such as disturbances in eating, sleeping, restlessness, or anxiety.

WHAT ARE THE RISKS OR HARMS OF PARTICIPATING IN THIS STUDY?

Like all medicines, the medicines studied in the trial and remimazolam may cause side effects.

Common side effects (which may affect more than 1 person out of 100 persons):

- Dyskinesia (emergence)
- Dizziness (emergence)
- Hypotension
- Respiratory depression
- Elevated blood bilirubin
- Elevated unbound bilirubin
- Vomiting

Detailed side effects can be found in the specification.

In addition, all subjects in this study received general anesthesia. Propofol offers deep sedation with quick onset and recovery, while there are still several side effects, including cardiorespiratory depression and injection pain. Sufentanil, an intravenous anesthetic, is an opioid and has specific side effects, such as respiratory depression, nausea, vomiting, constipation, and itching.

Contact the study doctor immediately if you experience any of these symptoms.

WHAT ARE THE BENEFITS OF PARTICIPATING IN THIS STUDY?

If you participate in this study, you may have a 1/2 chance to experience a lower incidence of emergence delirium by using the study drug. The study drug may improve patient experience and quality of recovery. The information collected in this study may help to improve the care of children in the future who require sedation such as you.

IS THERE ANY INSURANCE PROVIDED?

Specific insurance from Fujian Provincial Hospital will cover all medical expenses that may be necessary as a result of problems related to the study drugs and any possible damage. The insurance policy does not cover any amount exceeding its limit of liability and operates only in case of claims for damages submitted within the terms referred in the policy.

WHAT HAPPENS IF YOU CHOOSE NOT TO PARTICIPATE?

You may refuse to participate or withdraw from the program at any time during the program without affecting your doctor's care. You will **not** be discriminated against or retaliated against, and your medical treatment and rights will **not** be affected. If you do not participate in the program or drop out of it, please get in touch with your doctor. It is in your interest to protect your health.

CAN YOU WITHDRAW FROM PARTICIPATING IN THE STUDY ONCE YOU ARE ENROLLED?

You may choose to end participation in the study at any time without providing a reason and without affecting the quality or timeliness of your care. However, the research team will retain data obtained before your exit for analysis. It is essential that we collect information on participants who withdraw from the study to detect any side effects.

CAN YOUR DOCTOR WITHDRAW YOU FROM THE STUDY ONCE YOU ARE ENROLLED?

Your doctor or a research member may stop your participation in the study prematurely and without your consent for the following reasons:

1. The occurrence of a side effect, laboratory abnormality, or other medical condition in which continued participation in the study would be detrimental to your health.
2. If you are found to meet a study exclusion criterion (either newly developed or not previously recognized).

If you are removed from this study, the study doctor or member of the research team will discuss the reasons with you, and plans will be made for your continued care outside of the study.

Do you HAVE TO PAY FOR THE STUDY?

Your payment will not cover the anesthesia technology used in this study. If you are combined with the treatment and examination required for other diseases and switch to different treatments because the treatment is not adequate, the payment will not be free of charge. We

will observe the possible side effects/adverse reactions caused by the drug treatment in this study through regular follow-up after surgery and take measures to prevent and cure them. In case of any adverse reactions related to the drug in this study, the researcher will be responsible for the treatment and examination needed.

ARE STUDY PARTICIPANTS PAID TO BE IN THIS STUDY?

Although you decide to participate in this study, you will **NOT** be paid a monetary reward.

HOW WILL PARTICIPANT INFORMATION BE KEPT CONFIDENTIAL?

Your medical records will be kept at the hospital, and researchers, research authorities, and ethics committees will be allowed access to the information they need for this study. Your identity will not be disclosed in any public report on the results of this study. We will do everything within the law to protect the privacy of your personal medical information.

WHICH INFORMATION WILL BE MADE PUBLIC?

After the research, you will be informed about the results obtained through this study from your doctor. When results are disclosed to the public, any confidential information (including your child's name) will not be revealed.

MANDATORY SAMPLE COLLECTION?

We are not collecting any samples in this study.

IS THERE A CONFLICT OF INTEREST?

There are no conflicts of interest to declare related to this study.

WHO DO PARTICIPANTS CONTACT FOR QUESTIONS?

If you have any questions about this project, please get in touch with Dr. Yao Yusheng at +86 13559939629. If you have any questions related to your rights or interests, or if you would like to report your difficulties, dissatisfaction, or concerns during the implementation of the project, or if you would like to provide comments and suggestions related to the project, please get in touch with the Medical Department and Medical Ethics Committee of Fujian Provincial Hospital (+86-0591-87557768-8821).

WHAT DO YOU HAVE TO DO TO TAKE PART IN THIS STUDY?

You will be asked to sign the informed consent form to confirm that you have read all the information and understood the aims, the potential risks, and the benefits of this clinical study. The signed informed consent form will be stored in the archives of the hospital. You will be provided a copy of the signed document.

WHO CAN ANSWER YOUR QUESTIONS ABOUT THIS STUDY?

This information has been provided by doctor <Doctor Yao Yusheng >_____.

SUBJECT'S STATEMENT:

- ☐ I hereby declare to have read and understood the foregoing information materials/I confirm they have been read to me.
- ☐ I have had the opportunity to ask questions about the trial, and they have been answered to my satisfaction.
- ☐ I confirm that due time was given to me to make the decision.
- ☐ I am aware that participation in this study is entirely voluntary. I know I can decide at any time to stop my participation without having to explain why and without prejudice in terms of medical care.
- ☐ I consent that I will undergo a phone call.
- ☐ I am aware that some people will need to review my personal data as described in the information document. I allow access to my medical records and data by authorities and other personnel bound to medical secrets, as described in the information document.
- ☐ I consent to the use of the personal data of mine for the purposes that are described in the consent information document.
- ☐ I consent that the research data are stored according to national legislation.

Father's Signature：_____ Time (24 hr clock)：__ Date：_____

Mother's Signature：_____ Time (24 hr clock)：__ Date：_____

In case of legally authorized representative:

Legal authorized representative's signature: _____

Time (24 hr clock)：_____ Date：_____

Investigator's signature: _____ Time (24 hr clock)：__ Date：_____

Statement by the investigator/person taking consent

I confirm that I have accurately informed the patient and his/her parents about the Remimazolam trial. I have given the opportunity to ask questions and answer questions to

satisfaction.

I hereby confirm that the parents/legally authorized representative have/has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this Information Consent Form has been provided to the participant's parents/legally authorized representative.

Signature of investigator/person taking the consent: _____

Time (24 hr clock)：_____ Date：_____