Buddhist Tzu Chi Medical Foundation Hualien Tzu Chi Hospital

Clinical Trial Informed Consent Form

Revised Version of the Research Ethics Committee Meeting on November 28, 2023

Research Project Title

Exploring Novel Therapeutic Approaches for Disorders of Gut-Liver-Brain Interaction: Impact on Gastrointestinal and Psychological Symptoms as well as Pathophysiological Alterations

Trial Institution: Gastroenterology Department, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundatio n	Sponsoring Organization/Pharmaceutical Company: None Source of Research Funding: Hualien Tzu Chi Hospital

Principal Investigator: Wong, Ming-Wun	Organization/Position: Department: Gastroenterology / Attending Physician
Co-Principal Investigator: Chen, Chien-Lin	Organization/Position: Gastroenterology Department/Director
Co-Principal Investigator: Yi, Chih-Hsun	Organization/Position: Department: Gastroenterology / Attending Physician
Co-Principal Investigator: Liu, Tso-Tsai	Organization/Position: Gastrointestinal Function Testing/Director
Co-Principal Investigator: Lei, Wei-Yi	Organization/Position: Department: Gastroenterology / Attending Physician
Co-Principal Investigator: Hung, Jui-Sheng	Organization/Position: Department: Gastroenterology / Attending Physician
Co-Principal Investigator: Cheng, Chiu-Hsuan	Organization/Position: Cytopathology Department / Director

24-Hour Plan Contact Person：Wong, Ming-Wun　　Telephone：0982-098812

Research Subject's Name：_____　　Medical Record Number：_____

You have been invited to participate in this clinical trial. This form provides relevant information about the trial. The principal investigator or their authorized personnel will explain the details of the trial and answer any questions you may have. Please do not sign this consent form until all your questions have been satisfactorily answered.**You do not need to make an immediate decision about participating in this trial. Please sign only after careful consideration. You must sign the consent form to participate in this trial.**If you agree to participate, this document will serve as a record of your consent. **Even after agreeing, you can withdraw from the trial at any time without providing any reason.**

A. Objective of the Tria

This trial is a single-center clinical study in Taiwan, expected to be conducted for one year, with recruitment to conclude by December 31, 2025. The study plans to recruit 45 participants with functional dyspepsia from the Gastroenterology and Hepatology outpatient clinic.

The objective of this trial is to investigate the efficacy and pathological changes of antihistamine drugs on functional dyspepsia symptoms through a randomized controlled trial design.

All treatments carry risks, and clinical trials are no exception. Please carefully consider whether to participate in this trial.

B. Research Background or Current Status of the Drug/Medical Technology/Medical Device

Disorders of Gut-Brain Interaction, DGBI

Functional dyspepsia (FD) is associated with inflammatory responses caused by the release of histamine from eosinophils and mast cells, leading to increased intestinal mucosal permeability, which is a key pathogenic mechanism. Meta-analyses have shown that H2 antihistamine drugs are as effective as proton pump inhibitors in treating FD, while

H1 antihistamines achieve an efficacy rate of up to 79%. However, there is no research comparing the effects and pathological changes of combined H1/H2 antagonists versus single H1 antagonists in the treatment of functional dyspepsia.

Recent studies have shown that fatty liver disease and irritable bowel syndrome (IBS) share common comorbid factors, including obesity, gut microbiota, dietary factors, and immune-mediated causes. This has raised interest in whether these two conditions co-exist in patient populations. Moreover, the prevalence of IBS is higher in patients with fatty liver disease compared to global prevalence rates. A recent study found that up to 55.6% of patients with fatty liver have IBS, and it further suggests that patients with both IBS and fatty liver experience a lower quality of life and more severe physical and psychological symptoms.

1. **Famotidine 20mg/tab**
   (1) Product Information:
   This product is used for the treatment of peptic ulcers and gastroesophageal reflux disease (GERD). It competitively inhibits histamine at the H2 receptors on gastric parietal cells, thereby reducing gastric acid secretion (Ministry of Health and Welfare Drug License No. 041352).
   (2) Market Approval Status:
   Approved indications by the Ministry of Health and Welfare: gastric ulcers, duodenal ulcers, anastomotic ulcers, upper gastrointestinal bleeding, reflux esophagitis, and Zollinger-Ellison syndrome.

2. **Levocetirizine 5mg/tab**
   (1) Product Information:
   This is an antihistamine used to relieve various symptoms of allergies. Levocetirizine is an antihistamine that selectively competes with histamine at the H1 receptor sites on effector cells in the gastrointestinal tract, blood vessels, and respiratory system (Ministry of Health and Welfare Drug License No. 023792).
   (2) Market Approval Status:
   Approved indications by the Ministry of Health and Welfare: Treatment of various allergic symptoms caused by allergic rhinitis, chronic urticaria, and other conditions in adults and children aged six years and older.

3. **"Fuyuan" Gasmin Tablets 40mg/tab**
   (1) Product Information:
   This product appears as a round, white tablet. It works in the gastrointestinal tract by reducing the surface tension of gas bubbles, causing the bubbles attached to the gastrointestinal mucosa to rupture due to the change in tension. This facilitates the expulsion of gas from the body through belching or flatulence. (Taiwan FDA Drug License No. 000415).
   (2) Market Approval Status:
   Approved indications by the Ministry of Health and Welfare: Relief of bloating and alleviation of symptoms related to gas retention.

C. The main inclusion and exclusion criteria for the trial

The physicians or relevant research personnel conducting this study will discuss the necessary conditions for participation with you. Please cooperate and honestly provide us with your past health history. If you do not meet the criteria for participation, you will not be able to join the study.

1. Inclusion Criteria (Conditions for participation in this study):

(1). Aged between 18 and 64 years, conscious, and willing to sign the informed consent form.

(2). Meets the definition of functional dyspepsia: Chronic upper gastrointestinal symptoms (at least once a week, persisting for at least three months, with the first occurrence at least six months ago), including postprandial bloating, early satiety, epigastric pain, or burning sensation in the upper abdomen, with no abnormalities found on upper gastrointestinal endoscopy.

2. Exclusion Criteria (If you have any of the following conditions, you will not be able to participate in this study):

(1) Have undergone upper gastrointestinal surgery in the past two months.

(2) Currently undergoing antibiotic treatment for an infectious disease.

(3) Pregnant or breastfeeding women.

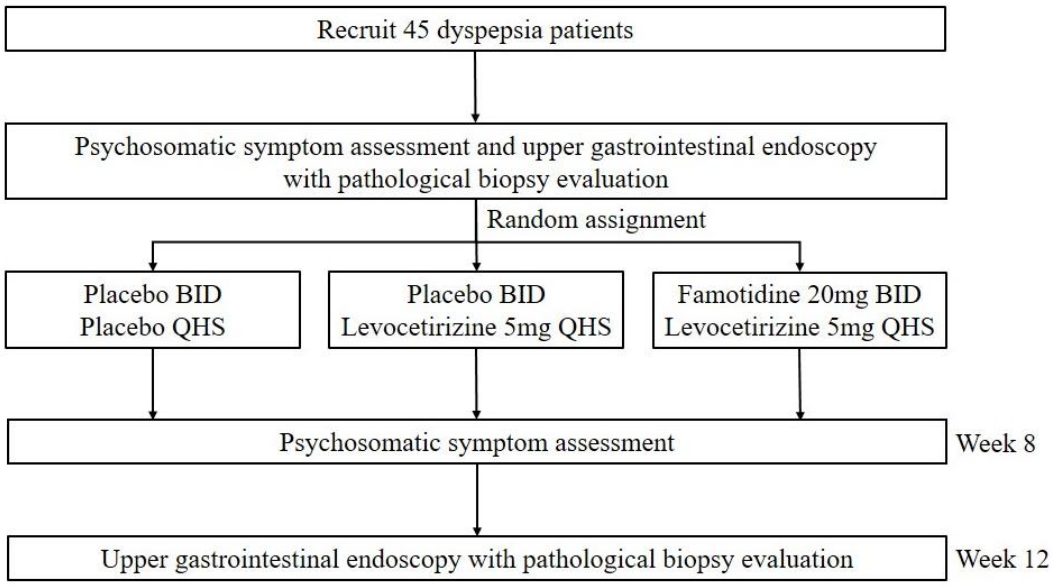
(4) Individuals with myocardial ischemia or those who have recently experienced a myocardial infarction.

(5) Individuals who are unable to cooperate.

D. Methods and Procedures of the Study

If your conditions meet the criteria and you decide to participate in this study and sign the consent form, we will proceed with the trial. First, you will complete a questionnaire assessment, including mental health, stress, and disease-related questionnaires, which will take approximately 20 minutes. The questionnaires will be anonymous. Following this, an upper gastrointestinal endoscopy will be arranged as the basis for diagnosing functional dyspepsia. Three tissue samples will be taken from the duodenum for eosinophil counting. You will then be randomly assigned to one of three treatment groups: (1) H1/H2 combination antagonist group: Famotidine 20mg twice daily + Levocetirizine 5mg once before bed; (2) H1 antagonist only group: placebo twice daily + Levocetirizine 5mg once before bed; (3) control group: Placebo (Fuyuan) once before bed + Placebo (Fuyuan) twice daily. After eight weeks of treatment, a reassessment of mental health symptoms will be conducted, and after twelve weeks, another upper gastrointestinal endoscopy will be performed for pathological evaluation. ◦

Trial Procedure Flowchart:



E. Potential Risks, Their Incidence, and Management Methods:

During the trial period, the study physician and other trial personnel will regularly monitor you for any adverse effects. If necessary, additional visits and tests will be arranged. If you experience any adverse effects, please inform the study physician and other trial personnel. The study physician will determine the appropriate treatment based on your condition.

1. Upper gastrointestinal endoscopy is basically relatively safe. If there is abdominal discomfort, most of them can be resolved by themselves. Depending on the situation, gastric emulsion tablets or intravenous injection of oxycodone can be given.
2. If there is a long interval between writing this book, please forgive me. If you have any questions, please feel free to inform the study host or other researchers. We will respect your wishes.
3. Possible risks associated with duodenal examination include sore throat, pain, aspiration pneumonia, dyspnea, arrhythmia or perforation in a small number of patients, but the incidence rate is less than 0.5%. Most patients may experience these diseases after the examination.
4. Possible side effects of famotidine (famotidine anti-film clothing box) after delivery: vomiting,

dizziness, vertigo, abdominal pain, constipation, leukemia reduction, rash; levocetirizine (levocetirizine anti-film clothing box) Clothes box) Possible side effects after delivery: drowsiness, dry mouth, stomach pain or nausea. If you have any of the above discomfort, please inform your doctor and stop using it; Placebo possible side effects: stomach constipation, stomach discomfort, diarrhea, abdominal pain ,vomit.

5. Medical staff will monitor your condition at all times after the test and provide immediate treatment.

If you experience any of the serious or dangerous side effects mentioned above, you should promptly:

1. Call the 24-hour emergency contact person.
2. Go to the nearest emergency room if necessary.

F. Alternative Therapies and Explanations

You are not obligated to participate in this study. If you choose not to participate, your physician will use standard diagnostic methods (such as upper gastrointestinal endoscopy, high-resolution impedance esophageal manometry, and 24-hour esophageal pH-impedance monitoring) to assess your symptoms and provide appropriate medical treatment.

G. Expected Benefits of the Trial

This trial will investigate the efficacy of antihistamine medications on the symptoms and pathological changes of functional dyspepsia, providing valuable references for both domestic and international research and clinical applications.

H. Contraindications, restrictions and matters that subjects should cooperate with during the trial:

During your participation in this trial, for your safety, please cooperate with the following matters:
Within 48 hours before upper gastrointestinal endoscopy, you should stop taking medications that may affect esophageal motility, such as Mosooweiqing Film-Coated Tablets, Yutuning Tablets, Weiminglang Film-Coated Tablets, etc. You are asked to fast for 8 hours before the examination. You cannot eat anything but can drink a small amount of water.
- For your own safety, if you experience any uncomfortable symptoms, illness, adverse effects or abnormal conditions during the trial, whether or not you think they are related to the trial, you should notify your trial physician.
- If you have any questions, please feel free to ask them directly to your trial staff (doctor, nurse, assistant).

I. Confidentiality of Participant's Personal Data:

Hualien Tzu Chi Hospital will handle any records and personal privacy data that can identify you as confidential in accordance with the law and will not disclose it. The researchers will use a research code to represent your identity, and this code will not show your name, national identification number, address, or any other identifiable information. If the trial results are published, your identity will still remain confidential. You also understand that by signing this consent form, you agree that your original medical records may be directly reviewed by monitors, auditors, the Hualien Tzu Chi Hospital Research Ethics Committee, and regulatory authorities to ensure that the clinical trial process and data comply with relevant laws and regulations. The above-mentioned personnel are committed to not violating the confidentiality of your identity. Except for the organizations authorized by law to review the data, we will carefully protect your privacy.

J. Withdrawal and Termination of the Trial

You are free to decide whether to participate in this trial, and you may withdraw or terminate your consent at any time during the trial without providing any reason. This will not result in any unpleasantness or affect your future medical care by the physician. **For your safety, you must withdraw from the trial if the following situations occur**:

1. Any discomfort, illness, or abnormal condition occurring during the trial.
2. Side effects caused by the medication。

If important new information arises during the course of the trial (that is relevant to your interests or affects your willingness to continue participating), you will be notified and given further explanation. You may reconsider whether to continue participating, and you are free to make that decision without any negative consequences or affecting your future medical care by the physician.

The principal investigator may also terminate the entire trial if necessary.

When you withdraw from the trial or the investigator determines that you are not suitable to continue, you will have the option to decide how to handle the samples you provided previously, as well as whether to agree to the investigator or sponsor continuing to collect your data.

1. Regarding the samples you previously provided:

   ☐ I agree to continue authorizing the use of the samples in this trial for research related to the disease in this study. Any use beyond the original written consent scope will require my consent again.

   ☐ I do not agree to continue authorizing the use of the samples in this trial, but to ensure the accuracy of the completed tests, I agree that the trial-related samples can be re-examined by the laboratory before being destroyed。

   ☐ I do not agree to continue authorizing the use of my samples in this trial. Please destroy my samples from the date of my withdrawal。

2. After withdrawal, I allow the trial principal investigator to continue collecting my data, such as obtaining my subsequent medical records and laboratory test results. During the data collection period, my privacy and personal data confidentiality will still be maintained.

   ☐ Agree to collect。

   ☐ Do not agree to continue collecting or reviewing my data for this trial.

K. Damage compensation and insurance

There are risks associated with the trial. To ensure protection in the event of adverse reactions resulting from participation in the trial, please carefully review the following information:

1. If damage occurs due to adverse reactions based on the clinical trial plan of this study, Hualien Tzu Chi Hospital will be responsible for compensation. However, adverse reactions that are listed in the informed consent as expected will not be compensated.
2. If damage or adverse reactions occur based on the clinical trial plan of this study, the hospital is willing to provide professional medical care and medical consultation. You will not be responsible for the necessary medical costs for treating these adverse reactions or damage.
3. Apart from the compensation and medical care mentioned in the previous two points, this study does not offer any other form of compensation. If you are unwilling to accept these risks, please refrain from participating in the trial.
4. Signing this consent form will not result in the loss of any legal rights.
5. This study has not taken out insurance for human clinical trial liability.

If you suffer damage due to an adverse reaction caused by your participation in this trial, the aforementioned compensation will include reasonable medical costs, provided that the following conditions are met: you used the trial medication according to the instructions of the trial physician; the damage was not intentionally caused; and you followed the medical advice of the trial physician.

L. Storage, Use, and Reuse of Participants' Samples (Including Derivatives) and Personal Data

1. Storage and Use of Samples (Including Derivatives) and Personal Data

The samples and related information you provide will be used for this research project and stored at the Gastroenterology Functional Examination Department of Hualien Tzu Chi Hospital until December 31, 2028. After the retention period, they will be legally destroyed. To protect your personal privacy, we will use a research identification number in place of your name and related personal information to ensure that your samples and associated data remain confidential.

If you have any concerns regarding the use of your samples and related data or wish to request their destruction, please contact us immediately (Contact: Dr. Ming-Wen Weng; Unit: Gastroenterology Functional Examination Department; Phone: 0982-098812; Address: No. 707, Section 3, Central Road, Hualien City). We will destroy your samples and related information upon your request. You may also contact the Research Ethics Committee of Hualien Tzu Chi Hospital (Phone: 03-8561825 ext. 12124) to assist you with any issues related to the use of samples and personal data in research.

2. Storage and Reuse of Remaining Samples

This research will not store remaining samples for reuse. Your samples will be destroyed once the retention period has expired.

M. Subject's Rights

1. If you have any doubts about the nature of the trial or concerns regarding your rights as a patient or if you suspect harm from participating in the study, you may contact the Hualien Tzu Chi Hospital Institutional Review Board for consultation at 03-8561825 ext. 12124.
2. During the trial, any significant findings related to your health or condition that may affect your willingness to continue participating in the clinical trial will be immediately provided to you. If you decide to withdraw, your physician will arrange for you to continue receiving medical care. If you decide to continue participating in the study, you may need to sign an updated consent form.
3. To participate in the study, you will need to be under the care of Dr. Ming-Wen Weng. If you have any questions or concerns now or during the trial, please feel free to contact Dr. Ming-Wen Weng at Hualien Tzu Chi Hospital, Department of Gastroenterology (24-hour contact: 0982-098812).
4. As a compensation for your time and travel expenses related to participation in the trial, you will receive a subsidy of NT$3,000 after signing the consent form and another NT$3,000 after the completion of the trial, for a total subsidy of NT$6,000.
5. If, within two years after the completion of the trial, any unexpected findings that directly affect your safety arise, you will be notified.
6. This consent form is provided in two copies, one for you and one for the trial sponsor. The trial principal investigator or authorized personnel has given you a copy of the consent form and fully explained the nature and purpose of the study. The physician has answered all of your questions regarding the medications and the study. ◦

I confirm that I have received a copy of the consent form.

Signature:_____ Date:____/___/___

N. Potential Commercial Benefits Derived from This Study

This study is not expected to generate any patent rights or other commercial benefits.

O. Explanation of Consent Form Signing

1. The consent form should be explained to the research participants by the principal investigator or their authorized personnel, addressing all questions raised by the participants. After providing the explanation, the investigator should sign and date the form first. Subsequently, the research participant or their representative should be given time to consider before signing the form.
2. When the legal guardian, authorized representative, or guardian signs the consent form:

✻According to Article 79 of the Medical Care Act, Article 12 of the Human Research Act, Article 5 of the Good Clinical Practice for Drug Trials, Section 6 of the Guidelines for the Collection of Human Biological Samples for Research, and Articles 13 and 15 of the Civil Code:

(1). For participants who lack legal capacity (such as minors under the age of 7 or individuals who have been declared legally incompetent), the legal guardian will sign on their behalf. If the participant has been declared legally incompetent, their guardian will serve as the legal representative.

(2). For participants with restricted legal capacity (such as minors over the age of 7, or individuals with mental disorders or other cognitive impairments that significantly impair their ability to make decisions or understand the consequences of their decisions, and who have been declared in need of assistance by a court), both the participant's consent and that of the legal guardian or assistant are required.

(3). For participants who are not legally incapacitated but may be unconscious or have mental and cognitive disorders that prevent effective communication and judgment, consent must be obtained from the authorized representative. The authorized representatives may include the participant’s spouse or cohabiting relatives.q

(4). For fetal research participants, the mother must provide consent.

(5). For posthumous biological samples, consent must be obtained from the participant's nearest relative or written consent obtained while the individual was alive.

3. Timing of Witness Signature:

✻Article 21 of the Good Clinical Practice Guidelines / Article 3 of the Civil Code:

(1). If the participant, legal representative, or person with consent authority is unable to read, a witness must be present to participate in all discussions regarding the participant's consent form. The witness should read the consent form and any other written materials provided to the participant, to ensure that the research investigator or designated personnel have thoroughly explained the contents and that the participant, legal representative, or person with consent authority fully understands all the information.

(2). The participant, legal representative, or person with consent authority should still personally sign and date the consent form. However, they may substitute a thumbprint for a signature.

(3). After the verbal explanation has been completed and the witness has confirmed that the participant, legal representative, or person with consent authority has freely given their consent, the witness should sign and date the consent form.

(4). Research-related personnel cannot serve as the witness.

(5). If a thumbprint, cross, or other symbol is used in place of a signature, two signatures must confirm this on the document, and it will have the same legal effect as a signed signature.

4. Article 12 of the Human Subjects Research Act:

✻The research participant must be an adult with the capacity to consent, unless the participant is a fetus or a cadaver. However, if the research is particularly beneficial to a specific population or cannot be substituted with other participants, this limitation does not apply. When the participant is an adult as mentioned in the previous clause, the consent of their family members should be obtained in the following order:

(1). Spouse
(2). Adult children
(3). Parents
(4). Siblings
(5). Grandparents

The written consent from the family members listed above can be given by one person. If there is a disagreement among the family members, the order of consent is determined according to the sequence listed above. For family members within the same category, the closer relative (in terms of degree of kinship) should be prioritized. If the degree of kinship is the same, the cohabiting relatives should be prioritized, and if there are no cohabiting relatives, the elder family members should be given priority.

P. Signature

1. The principal investigator, co-investigator, or their authorized personnel have provided a detailed explanation of the nature and purpose of the research methods described above, as well as the potential risks and benefits associated with this study.

Principal Investigator/Co-Investigator Signature: _____

Date:_____/____/____

Signature of Other Research Personnel Involved in the Explanation and Discussion of the Consent Process: _____

Date:_____/____/____

2. After the explanation, I fully understand the research methods described above and the potential risks and benefits. All my questions regarding this research study have been thoroughly addressed. I agree to participate in this study voluntarily and will retain a copy of the consent form.

Research Participant Signature：_____

Date:_____/____/____

Date of Birth:_____/____/_____

Phone Number:_____

ID number:_____Gender:_____

Correspondence Address:_____

＊ When the case subject meets the requirements of Item 2 in the [Consent Form Signing Instructions], this field must be completed with a signature.

3. **Signature of Legal Representative/Authorized Consenter:：_____**

Date:_____/____/____

Relationship to the Research Subject (Please circle): Spouse, Father, Mother, Son, Daughter, Other:_____

Correspondence Address:_____

＊ If the subject of the study meets the conditions described in Item 3 of the "Consent Form Signing Instructions," this section must be completed and signed.

4. **Witness 1 Signature：_____**

Date:_____/____/____

Contact Phone Number：_____

Witness 2 Signature：_____

Date:_____/____/____

Contact Phone Number：_____