Single center, Open Label, controlled Study to assess the safety & efficacy of Oral Ciprodiazole ® Tablets (Ciprofolxacin/ Metronidazole) versus currently used Ciprofloxacin Tablets & Metronidazole tablets in pelvi-abdominal infections and following IV antibiotics in post-operative period, for pelvi-abdominal surgeries or acute conditions

Clinical Study Protocol No.: CIPRO-001

Version 1- amendment 1

Dated 20 Mar 2022

Sponsor: MINAPHARM Pharmaceuticals

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Trial Protocol Agreement

Protocol Name: Single center, Open Label, controlled Study to assess the safety & efficacy of Oral Ciprodiazole ® Tablets (Ciprofolxacin/Metronidazole) versus currently used Ciprofloxacin Tablets & Metronidazole tablets in pelvi-abdominal infections and following IV antibiotics in post-operative period, for pelvi-abdominal surgeries or acute conditions

Clinical Study Protocol No.: CIPRO-001

Version: 1 Amendment 1

Dated: 20 March 22

I,……., the Investigator, have read and understood the above-referenced Minapharm Pharmaceuticals study Protocol and have fully discussed the objectives of this observational study and the contents of this protocol with the sponsor's team.

I agree to conduct according to this study protocol and to comply with its requirements, ethical and safety considerations.

I understand that, should the decision be made by the sponsor to terminate prematurely or suspend the study at any time for whatever reason; such decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate such decision in writing to the Sponsor.

INVESTIGATOR	SPONSOR
Name: Ahmed Farag El Kased	Name: Doris Ezzat
Title:	Title: Clinical department Head
Date:	Date:
Signature:	Signature:

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1 Responsible Parties

1.1.Sponsor:

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Sponsor Responsible Personnel:

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1.2 1.3 Principal investigators:

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1.3 1.4 Coordinating investigators:

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2 Study Abstract

TITLE	Single center, Open Label, controlled Study to assess the safety & efficacy of Oral Ciprodiazole ® Tablets (Ciprofloxacin/Metronidazole) versus currently used Ciprofloxacin Tablets & Metronidazole tablets in pelvi-abdominal infections and following IV antibiotics in post-operative period, for pelvi-abdominal surgeries or acute conditions
CLINICAL STUDY PROTOCOL NUMBER & VERSION	CIPRO-001 Version 1 - Dated 15 Nov 2018
MAIN AUTHOR NAME & AFFILIATION	Lydia Bahig Clinical Research Associate, Nagy Research CRO
PHYSICIANS/ LOCATION	Principle Investigator: Dr. Ahmed Farag El Kased Location: Menoufia University Hospital
RATIONALE & BACKGROUND	Ciprodiazole (Ciprofloxacin & Metronidazole) is active against a broad spectrum of obligate anaerobic bacteria, including Bacteroids Species (spp.), Fusobacterium spp., Clostridium spp., Treponema spp. and various anaerobic cocci. The action is trichomonicidal, and bactericidal. So, it is indicated in the treatment of Pelvi-abdominal infections caused by gram negative bacteria such as E. coil, Pseudomonas aeruginosa, Proteus mirabilis, Klebsiella pneumonia, Bacteroides fragilis or others. In this study, we compare the safety and efficacy of oral Ciprodiazole 500 mg (Ciprofloxacin /Metronidazole) versus currently used Ciprofloxacin Tablets & Metronidazole tablets in pelvi-abdominal infections and following IV antibiotics in post-operative period, for pelvi-abdominal surgeries or acute conditions
RESEARCH QUESTION & STUDY OBJECTIVES	**Primary Objectives:** 1) Primary Safety: To compare safety of oral Ciprodiazole ® tablets (Ciprofloxacin/Metronidazole) versus currently used Ciprofloxacin Tablets & Metronidazole tablets for pelvi-abdominal infections, either non-operative or post-operative following IV antibiotics.

	2) Primary Efficacy: To compare efficacy of oral Ciprodiazole ® tablets (Ciprofolxacin/Metronidazole) versus currently used Ciprofloxacin Tablets & Metronidazole tablets for pelvi-abdominal infections, either non-operative or post-operative following IV antibiotics. **<u>Secondary Objective</u>** 1) Secondary Safety: - Presence of any signs/symptoms of post-operative wound infection such as redness, fever or wound discharge. - Presence of undesirable effects on total leukocyte count and liver enzymes (SGOT & SGPT) 2) Secondary Efficacy: - To compare the complete resolution or improvement of Pelvi-abdominal infection between ciprodiazole® versus combined treatment, based on pelvi-abdominal ultrasound and others - To compare the days for complete healing of post-operative wounds between ciprodiazole® versus combined treatment
STUDY DESIGN	Comparative, randomized, Single center, Open label study to compare the safety and efficacy of oral Ciprodiazole 500 mg (Ciprofloxacin /Metronidazole) versus currently used Ciprofloxacin Tablets & Metronidazole tablets in pelvi-abdominal infections and following IV antibiotics in post-operative period, for pelvi-abdominal surgeries or acute conditions A study population of 312 patients who had pelvi-abdominal infection or started IV antibiotics for 48 hours, post-operative or till be able to tolerate oral intake in post-operative period, for pelvi-abdominal surgeries or acute conditions. They will be randomized by computer, to receive Ciprodiazole ® tablets (Ciprofloxacin/Metronidazole) versus currently used Ciprofloxacin Tablets & Metronidazole tablets for a duration not exceeding 15 days
STUDY DURATION	➢ Subjects will be enrolled for 12 months including screening visit ➢ Follow up for 15 days from enrolment
STUDY POPULATION	312 Egyptian Patients with pelvi-abdominal infection or started IV antibiotics in post-operative period, for pelvi - abdominal surgeries and/or acute conditions
	Inclusion Criteria: 1. Egyptian male and female patients aged between 18-65

SELECTION CRITERIA	years' old 2. Subjects having pelvi-abdominal infections such as and not limited to: Ulcerative Colitis, Diverticulitis, Cholecystitis and Pelvic Inflammatory Diseases (PID), as oophoritis and salpingo-oophoritis. 3. Subjects during post-operative period for pelvi-abdominal surgery and following IV medication with Metronidazole injection plus third generation cephalosporin. 4. Subjects who are willing to sign Informed Consent Form (ICF) and ready to comply with the protocol for the duration of the study ***Exclusion Criteria:*** 1. Subjects with a history of hypersensitivity to any of the active ingredients of the treatments used 2. Subjects who are receiving or received any other antibiotics during the previous two weeks, rather than IV treatment in the first post-operative 48 hours, mentioned in the protocol 3. Subjects with Pelvi-abdominal infection and performed surgery after failure of oral antibiotics. 4. Subjects having surgeries such as colorectal surgeries. 5. Subjects with any medical condition requiring the usage of the following medications: -Drugs that induce microsomal liver enzymes, such as Phenytoin or Phenobarbital. -Drugs that decrease microsomal liver enzymes activity, such as cetrimide. -Theophylline -Corticosteroids -Antacids containing magnesium and aluminum, supplements and other products containing calcium, iron or zinc -Tizanidine 6. Subjects with uncontrolled diabetes mellitus; FBG > 200 mg/ml 7. All subjects with renal impairment (S. Creatinine > 1.5 mg/dL) 8. All subjects with hepatic impairment (Child-Pugh Score B-C) 9. Subjects with liver enzymes (SGOT & SGPT > 2 Normal range)

	10. Pregnant or breast feeding women
MEDICINAL PRODUCT	Ciprodiazole ® Tablets (Ciprofloxacin hydrochloride 500 mg & Metronidazole 500 mg)
VARIABLES	<u>Primary Endpoints:</u> 1- Primary Safety: - Incidence of serious/non-serious adverse events 2- Primary Efficacy: - Complete resolution for pelvi-abdominal infection based on pelvi-abdominal ultrasound and others and/or clinical response - Complete healing of the of post-operative wounds <u>Secondary Endpoints:</u> 1- Secondary Safety: - Presence of any signs/symptoms of post-operative wound infection such as redness, fever or wound discharge. - Change in Total Leukocyte count and Liver enzymes (SGOT, SGPT) between baseline (visit 1) to End of study visit (Follow up 2 V) 2- Secondary Efficacy: - Describe complete resolution, improvement, failure or relapse of pelvi-abdominal infection based on pelvi-abdominal ultrasound and others and/or clinical response - Days for complete healing of post-operative wounds after 8 days of treatment (Follow-up 1 V) & 15 days of treatment (End of study visit) between the 2 groups
ASSESSMENT SCHEDULE	Subjects will be enrolled for 12 months including screening visit ➢ Visit 1: Screening and treatment initiation visit, Day 0 ➢ Follow-up 1 visit: Day 8 (+/-) 3 days ➢ Follow-up 2 visit & End of study visit: Day 15 (+/-) 3 days
DATA SOURCES	All visits' assessments will be kept in the source files for each patient and in Case Report Form (CRF), which will be verified by the responsible Clinical Research Associate (CRA).
STUDY SIZE	312 patients with pelvi-abdominal infection and/or who started IV antibiotics in post-operative period, for pelvi-

	abdominal surgeries. They will be randomized by computer, into 2 treatment groups; Ciprodiazole ® tablets (Ciprofloxacin/Metronidazole) versus currently used Ciprofloxacin Tablets & Metronidazole tablets, from the surgical department in Menoufia University Hospital and some patients might be referred from other departments in Menoufia University Hospital such as and not limited to; the department of Gynecology and Obstetrics
DATA ANALYSIS	Descriptive analysis of the collected data. All enrolled patients will be included in the safety analysis. All quantitative primary and secondary end point variables will be described Data from primary and secondary endpoints will be summarized using appropriate summary statistics i.e. Number of subjects (n), mean, Standard Deviation (SD), median and range.
STUDY MILESTONES	**Planned Timelines:** First Patient First Visit (FPFV): 01 March 21 First Patient First Treatment (FPFT): 01 March 21 Last Patient First Treatment (LPFT): 31 Dec 22 Last Patient Last Visit (LPLV): 15 January 23 Database Lock: 15 March 23 Final Study Report: 31 May 23

3 List of Abbreviations

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
AST	Aspartate Aminotransferase
CBC	Complete Blood Count
CRF	Case Report Form
CRO	Clinical Research Organization
DVT	Deep Vein Thrombosis
EOT	End of Treatment
EPVC	Egyptian Pharmaco Vigilance Center
FBS	Fasting Blood Sugar
FPFT	First Patient First Treatment
FPFV	First Patient First Visit
G6PD	Glucose-6-Phosphate Dehydrogenase
GCP	Good Clinical Practice
ICF	Informed Consent Form
INR	International Normalized Ratio
IAIs	Intra-Abdominal Infections
IRB	Institutional Review Board
ITT	Intention to Treat
LPLT	Last Patient Last Treatment
LPLV	Last Patient Last Visit
No.	Number of subjects
PID	Pelvic Inflammatory Diseases
PP	Per Protocol
PP	Post-operative Peritonitis
PT	Prothrombin Time
SAE	Serious Adverse Event
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SD	Standard Deviation
SIV	Site Initiation Visit
SPP.	Species
WHO	World Health Organization

4 Amendments & Updates

Not applicable

5 Study Milestones

- **Screening and Enrollment Period:** 12 months

  Planned Timelines:

FPFV Date	FPFT Date	LPFT Date	LPLV Date
01 Mar 21	01 Mar21	31 Dec 22	15 Jan 23

Database Lock Date	Final Study Report
15 March 23	31 May 23

6 Introduction & Background

Intra-Abdominal Infections (IAIs) include many pathological conditions, ranging from uncomplicated IAIs to complicated peritonitis; either localized peritonitis or diffuse peritonitis, depending on the ability of the host to contain the process within a part of the abdominal cavity. [1]

IAIs are also classified into community-acquired intra-abdominal infections (CA-IAIs) and healthcare-acquired intra-abdominal infections (HA-IAIs). CA-IAIs are acquired in community, while HA-IAIs develop in hospitalized patients or residents of long-term care facilities. They are characterized by increased mortality because of both underlying patient health status and increased likelihood of infection caused by multi drugs resistant organisms. [2]

The diagnosis of IAI is based primarily on clinical assessment. Classic symptoms of IAIs include abdominal pain and a systemic inflammatory response, including fever, tachycardia, and tachypnea. Abdominal rigidity suggests the presence of peritonitis.[3]

Patients with uncomplicated IAIs can be managed with either surgical source control or antibiotics alone, while the treatment of patients with complicated IAIs involves both source control and antibiotic therapy. [٢]

The most common Post-operative IAI is Post-Operative Peritonitis (PP). It is a life-threatening hospital-acquired IAI with high rates of mortality [4]. The most common cause of PP is an anastomotic leakage [5]. The diagnosis of PP may be difficult because there are no absolutely specific clinical signs and laboratory tests to reject or confirm the diagnosis. Treating patients with PP requires supportive therapy of organ dysfunction, source control of infection, and intensive antimicrobial therapy [3]

Pelvi-abdominal infections are the most communal infectious complications challenged by the surgeon. Actual managing needs prompt finding, well-timed and suitable clinical intervention and satisfactory antimicrobial treatment. Meanwhile nation results usually are not obtainable for the first 48 - ٧٢h next surgical procedure, experimental antimicrobial treatment necessity cover the most prospective pathogens, i.e. a combination of Gram-positive and Gram-negative aerobic and anaerobic bacteria that contain the typical flora of the gastrointestinal tract. Bacteroides fragilis and Escherichia coli are the two furthermost communal isolates in furthermost studies of intra-abdominal infections [6, 7, 8, 9]

Also, the most common postoperative complications are postoperative fever, postoperative infection, atelectasis, embolism and Deep Vein Thrombosis (DVT). Postoperative infections include postoperative sepsis, urinary tract infection, chest infection, peritonitis, pelvic abscess, and surgical site infection. The highest incidence of postoperative complications is between one and three days after the operation. However, specific complications occur in the following distinct temporal patterns: early postoperative, several days after the operation, throughout the postoperative period and in the late postoperative period. [10]

Pelvic inflammatory disease (PID) is one of pelvi-abdominal infections that ranges from acute salpingitis to salpingo-oophoritis and ultimately pelvic abscess, if the disease process proceeds unabated. Morbidity is high, 20% of affected women become infertile,[11] 30% develop chronic pelvic pain and around 1% of those who conceive have an ectopic pregnancy.[12] There are neither pathognomonic symptoms nor specific laboratory tests to diagnose PID. However, specimens from the vagina and cervix should be taken for direct microscopy, culture and sensitivity prior to starting empirical treatment. [13] In the absence of generalized peritonitis or septicemia, most PID patients may be treated initially with oral antimicrobials. When intravenous antimicrobials are initiated, they should be continued for 24 hours after clinical response before converting to oral therapy. A 14-day course is recommended for adequate treatment. Surgical intervention may be required to either confirm the diagnosis of PID or surgical drainage of pelvic abscesses. Also, it should be considered in the following conditions: clinical failure with oral therapy, severe PID, inability to tolerate an oral regimen and in pregnancy. [12 - 13]

7 Rationale & Correlative Studies

7.1 Rationale:

Ciprodiazole® (Ciprofloxacin & Metronidazole) is active against a broad spectrum of obligate anaerobic bacteria, including Bacteroids Species (spp.), Fusobacterium spp., Clostridium spp., Treponema spp. and various anaerobic cocci. The action is trichomonicidal and bactericidal. So, it is indicated in the treatment of Pelvi-abdominal caused by Gram negative bacteria such as E. coil, Pseudomonas aeruginosa, Proteus mirabilis, Klebsiella pneumonia, or Bacteroides fragilis or others.

In this study, we compare the safety and efficacy of oral Ciprodiazole 500 mg® (Ciprofloxacin /Metronidazole) versus currently used Ciprofloxacin Tablets & Metronidazole tablets in pelvi-abdominal infections and/or following IV antibiotics in post-operative period, for pelvi-abdominal surgeries or acute conditions

7.2 Correlative Studies:

The results of a randomized trial comparing sequential Intravenous (IV) / oral treatment with Ciprofloxacin plus Metronidazole to lmipenem/ Cilastatin for IAIs showed that Ciprofloxacin plus Metronidazole were found to be effective for the treatment of serious and complicated IAIs. In addition, sequential IV/ oral therapy with Ciprofloxacin plus Metronidazole was efficacious in patients able to tolerate oral intake.[14]

The comparison study of IV / oral Ciprofloxacin plus Metronidazole versus Piperacillin / Tazobactam in the treatment of complicated IAIs proved that initial administration of IV Ciprofloxacin plus Metronidazole followed by oral Ciprofloxacin plus Metronidazole therapy is clinically more effective than IV Piperacillin/Tazobactam for the treatment of patients with complicated IAIs. [15]

A meta-analysis of comparative trials of Ciprofloxacin/metronidazole versus β – lactam in treatment of IAIs suggested that the ciprofloxacin/metronidazole combination may be superior to β – lactam-based therapeutic regimens in the treatment of IAIs with regard to cure of infections, although no difference in mortality was found. [16]

8 Treatment:

The treatment will be prescribed in the usual manner in accordance with the terms of the local marketing authorization with regards to dose, population and indication.

8.1 Ciprodiazole ® Tablets:

Each film coated tablet of Ciprodiazole ® consists of Ciprofloxacin hydrochloride 500 mg, Metronidazole 500 mg, and excipients; pregelatinized starch, sodium starch glycolate, P.V.P K 30, lactose monohydrate 200 mesh, sodium lauryl sulphate, magnesium stearate, and wincoat green. It is indicated for Pelvi-abdominal infections caused by E. coli, Pseudomonas aeruginosa, Proteus mirabilis, Klebsiella pneumonia, or Bacteroides fragilis and diverticulitis. Ciprodiazole ® is manufactured by Minapharm under Marketing Authorization Number: 26357/2009, dated 01/10/2009

After oral administration, Ciprofloxacin is well absorbed from the abdominal tract. Oral bioavailability is approximately 70 % [17] and a peak plasma concentration of about 2.5 mcg per ml is achieved after 1 to 2 hours after a dose of 500 mg by mouth. Metronidazole is rapidly absorbed, 80 % is absorbed in one hour. The peak concentration is achieved after 1 to 2 hours after the oral administration. Metronidazole passes the placenta and the maternal milk. The essential excretion is through the liver and the bile. They are absorbed readily and almost completely from the gastrointestinal tract. Serum concentrations reach their peak within one hour of oral ingestion.

Ciprodiazole is contraindicated in the following conditions:

- Hypersensitivity to ciprofloxacin or other antibiotics of Quinolones group such as Orfloxacin, Norfloxacin, Trovofloxacin, and Ofloxacin.
- Hypersensitivity to the metronidazole or other nitroimidazole derivatives
- Children and adolescents below 16 years.
- Epilepsy or other seizure disorders.

- Patients with Glucose-6-Phosphate Dehydrogenase (G6PD) enzyme deficiency.

Sponsor will provide the study treatment for the patients' whole duration according to regulation of Local Health Authorities involved in the product supply since the drug is being used according to the approved marketing label.

The investigator and the research team must evaluate all adverse events and laboratory abnormalities during the study.

A drug-related toxicity or laboratory value outside of the reference range; that is judged by the investigator as having a "reasonable possibility" of being related to the study drug; will be considered as an adverse event.

Drug-Toxicity is deemed "clinically significant" based on the medical judgment of the investigator. Laboratory abnormalities will be managed as deemed clinically appropriate by the investigator until resolved.

The investigator should ensure that any study drug interruptions or dose modifications and associated adverse events are promptly entered into the medical records.

8.2 Ciprofloxacin Hydrochloride:

Ciprofloxacin is a synthetic broad spectrum fluoroquinolone antibiotic. It acts by inhibiting DNA gyrase, which is essential in the reproduction of bacterial DNA. This agent is more active against Gram-negative bacteria than Gram-positive bacteria and aerobic organisms commonly encountered in pelvi-abdominal infections. [18 - 19]

Ciprofloxacin is indicated for the treatment of the following infections caused by susceptible organisms: urinary tract infections, acute uncomplicated cystitis, chronic bacterial prostatitis, lower respiratory tract infections, acute sinusitis, skin and skin structure infections, bone and joint infections, complicated Pelvi-abdominal infections (used in combination with metronidazole)[١٤], infectious diarrhea, typhoid fever (enteric fever), uncomplicated cervical and urethral gonorrhea, inhalational anthrax (post-exposure), and to prevent infections occurring after operations.

Ciprofloxacin is well absorbed from the abdominal tract. Oral bioavailability is approximately 70% [17] and a peak plasma concentration of about 2.5 mcg per ml is achieved after 1 to 2 hours after a dose of 500 mg by mouth. The serum elimination half-life in subjects with normal renal function is approximately 4 hours. Approximately 40 to 50% of an orally administered dose is excreted in the urine as unchanged drug. [18]

Ciprofloxacin is contraindicated in subjects with a history of hypersensitivity to ciprofloxacin or any member of the fluoroquinolone class of antimicrobial agents. The most frequently reported drug related events, from clinical trials for all indications of ciprofloxacin therapy were nausea, diarrhea, liver function tests abnormality, vomiting, and rash.

8.3 Metronidazole:

Metronidazole belongs to a group of medicines called anti-infective agents. It may be used to treat infections, caused by bacteria of the blood, brain, bone, lung, stomach lining and pelvic area, following childbirth or an operation. Also, it is used to treat urinary or genital infections caused by Trichomonas Vaginalis, Gardnerella Vaginalis, Giardia lambia and Entamoeba histolytica, gum and teeth infections, infected leg ulcers or pressure sores, stomach ulcers caused by Helicobacter pylori or to prevent infections occurring after operations.

Metronidazole is a prodrug. Unionized metronidazole is selective for anaerobic bacteria due to their ability to reduce metronidazole to its active form. This reduced metronidazole then covalently binds to DNA, disrupt its helical structure, inhibiting bacterial nucleic acid synthesis and resulting in bacterial cell death.

After oral administration, Metronidazole is rapidly absorbed, 80 % is absorbed in one hour. The peak concentration is achieved after 1 to 2 hours after the oral administration. Metronidazole passes the placenta and the maternal milk. The serum elimination half-life in subjects is 8 hours. The essential excretion is through the liver and the bile.

The most common side effects include: allergic reactions such as skin rash, swelling of the face, lips, tongue or throat, fever or difficulty in breathing.

Metronidazole is contraindicated in case of Hypersensitivity to Metronidazole and First trimester of pregnancy, while it should be administered with caution to patients with the following conditions:

- Convulsive seizures and peripheral neuropathy
- Patients with active neurological disorders
- Decreased Neutrophils or a history of blood dyscrasias
- Prolonged QT interval on ECG
- Severe liver disease

8.4 Dosage & Administration:

8.4.1 Ciprodiazole ® Tablets:

The recommended dosage of ciprodiazole® is 1 tablet every 12 hours for a duration not exceeding 15 days, according to the investigator's decision. The tablet should be swallowed with plenty of water.

8.4.2 Ciprofloxacin ® Tablets:

The recommended dosage of Ciprofloxacin tablets is 500 mg every 12 hours for 7 to 14 days, according to the investigator's decision. Tablets should be swallowed with plenty of fluid, during or after meals. It is contraindicated to be taken with dairy products such as milk or yoghurt or with fortified fruit juices (e.g. calcium-fortified orange juice).

The usual dose of Ciprofloxacin should be modified in patients with severe renal impairment, as the following table of the dosage guidelines, according to the Creatinine Clearance (CrCl):

CrCl (mL/min)	**Dose**
> 50	Usual Dosage
30 – 50	250 – 500 mg every 12 h
5 – 29	250 – 500 mg every 18 h
Patients on hemodialysis or Peritoneal dialysis	250 – 500 mg every 24 h (after dialysis)

8.4.3 Metronidazole ® Tablets:

Tablets should be swallowed with plenty of water, during or after meals. The recommended dose is 7.5 mg/kg every 6 hours (approx. 500 mg for a 70-kg adult every 6 hours). A maximum of 4 g should not be exceeded during a 24-hour period for 7 to 10 days, according to the investigator's decision.

For patients with severe renal impairment (CrCl < 30), the dose of Metronidazole ® Tablets should be reduced by 50%

8.5 8.5 Precautions:

Fluoroquinolones are contraindicated with patients with known history of myasthenia gravis, because they have neuromuscular blocking activity and may exacerbate muscle weakness.

The overdose may lead to loss of appetite, diarrhea, metallic taste, headache, dizziness, insomnia or drowsiness.

The following is a list of possible side effects that may occur, rarely, from the use of Ciprodiazole ® tablets:

- Allergic reactions such as rash, itching, and swelling of the mouth, face, lips, or tongue
- Nausea, headache, anorexia, diarrhea, unpleasant metallic taste, stomach cramps pain, vomiting, fainting, and fever.
- Reversible neutropenia (leukopenia), and blood dyscrasias.
- Dysuria, darkening of urine, cystitis, bloody stools, abdominal and vaginal yeast infection.
- Tendon inflammation and damage.
- Irregular heartbeat and loss of consciousness.
- Mood or mental changes such as anxiety, confusion, depression, and sleeplessness.
- Convulsive seizures and peripheral neuropathy tremors.
- Jaundice.

8.5.1 Storage and Drug Accountability:

Study drugs are to be stored at room temperature up to 30 degrees C (86 degrees F). Keep them in the original containers. Store away from heat, moisture, and light. Do not store in the bathroom. Keep them out of the reach of children and away from pets.

All empty, partially used, and unused blisters will be retained by the Investigator (at room temperature) until they are returned to the pharmacist and to be checked by monitor.

8.5.2 Dispensing

The Sponsor will be responsible for providing the study drugs either Ciprodiazole ® Tablets (Ciprofloxacin/Metronidazole) or Ciprofloxacin Tablets & Metronidazole tablets to the patients in a quantity enough to be used till the end of the study and will record the patient's number and initials.

8.6 Risks & Benefits of study drug

Benefit: Ciprodiazole® (Ciprofloxacin & Metronidazole) is active against a broad spectrum of aerobic/anaerobic bacteria. So, it is indicated in pelvi-abdominal infections and/or following IV antibiotics in post-operative period, for pelvi-abdominal surgeries or acute conditions, it will be supplied by the sponsor.

Risk: The most frequently reported side effects of ciprofloxacin are nausea, diarrhea, liver function tests abnormality, vomiting, and rash.

The most common side effects of Metronidazole are allergic reactions such as skin rash, swelling of the face, lips, tongue or throat, fever or difficulty in breathing.

8.7 Discontinuation and Modification of Dosing of Ciprodiazole ®:

- The usual dose should be reduced in patients with severe renal disease
- In the event that a positive result is obtained on a pregnancy test for a patient, the administration of Ciprofloxacin and Metronidazole must be discontinued immediately.

8.8 Concomitant Medication:

Throughout the study, Investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in the exclusion criteria. If these are required, the participant will be withdrawn. A medication, other than the study medication (Ciprofloxacin or Metronidazole) taken during the study will be recorded in the CRF.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving from 2 weeks prior to study drug administration and during the study, must be recorded in the paper case report form along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency.

The investigator should review all concomitant medications for any potential interactions.

Ciprodiazole ® Tablets (Ciprofloxacin hydrochloride & Metronidazole) is contraindicated with administration of tizanidine, because this may cause low blood pressure and sleepiness

Ciprodiazole ® Tablets is contraindicated with administration of antacids containing magnesium and aluminum, supplements and other products containing calcium, iron or zinc because they reduce the effect of Ciprofloxacin.

Metronidazole potentiates the anticoagulant effect of Warfarin and other oral coumarin anticoagulants resulting in a prolongation of prothrombin time.

The simultaneous administration of drugs that induce microsomal liver enzymes, such as Phenytoin or Phenobarbital, may accelerate the elimination of metronidazole while the simultaneous administration of drugs that decrease microsomal liver enzymes activity, such as cetrimide, may prolong the half-life and decrease plasma clearance of metronidazole.

Ciprofloxacin may increase the effects of caffeine.

Serious and fatal reactions have occurred when Ciprofloxacin was taken in combination with theophylline. These reactions have included cardiac arrest, seizures, status epilepticus, and respiratory failure.

Tendon disorders (tendinitis) have been rarely encountered in some cases related to concomitant use of quinolone with corticosteroids.

9 Research Question & Study Objectives

9.1 Primary Objective:

9.1.1 Primary Safety:

To compare safety of oral Ciprodiazole® tablets (Ciprofolxacin/Metronidazole) versus currently used Ciprofloxacin Tablets & Metronidazole tablets in pelvi-abdominal infections, either non-operative or post- operative following IV antibiotics.

9.1.2 Primary Efficacy:

To compare efficacy of oral Ciprodiazole® tablets (Ciprofolxacin/Metronidazole) versus currently used Ciprofloxacin Tablets & Metronidazole tablets in pelvi-abdominal infections, either non-operative or post- operative following IV antibiotics

9.2 Secondary Objective:

9.2.1 Secondary Safety:

- Presence of any signs/symptoms of post-operative wound infection such as redness, fever or wound discharge.
- Presence of undesirable effects on total leukocyte count and liver enzymes (SGOT & SGPT)

9.2.2 Secondary Efficacy:

- To compare the complete resolution or improvement of Pelvi-abdominal infection between ciprodiazole® versus combined treatment, based on pelvi-abdominal ultrasound and others
- To compare the days for complete healing of post-operative wounds between ciprodiazole® versus combined treatment

10 Research Methods

10.1 Study Design:

This is a single center, open Label, controlled, interventional phase IV Study conducted in Menoufia University Hospital in Egypt to compare the safety and efficacy of oral Ciprodiazole® tablets (Ciprofloxacin/Metronidazole) versus currently used Ciprofloxacin Tablets & Metronidazole tablets in pelvi-abdominal infection and following IV antibiotics in post-operative period, for pelvi-abdominal surgeries or acute conditions

This study is a clinical trial that will enroll 312 patients, who had pelvi-abdominal infection and/or started IV antibiotics for 48 hours, post-operative or till be able to tolerate oral intake in post-operative period, for pelvi-abdominal surgeries. They will be divided into two

treatment groups; group A: patients are treated with Ciprodiazole ® tablets (Ciprofloxacin/Metronidazole) and group B (control group): patients are treated with the currently used Ciprofloxacin Tablets & Metronidazole tablets, using computer-generated randomization list, generated by the Data Management department (DM) of the CRO (Nagy Research) for the 2 groups who will be enrolled in this study will agree to the release of information and sign an informed consent. Subjects included in this study are enrolled for the collection of data that reflect the care they receive under routine clinical circumstances. All provided care should be according to protocol and the local standard of medical care.

The screening and enrollment period is planned to be 12 months. Subject will start receiving the treatment for a duration not exceeding 15 days. And with post-operative cases, subject will start receiving the treatment after IV antibiotics for 48 hours or till be able to tolerate oral intake. Follow up will be for 15 days from enrolment till End of treatment.

10.2 Study Setting:

Subjects will consent to the collection of study related information while on the study. Subjects will be informed that data will be collected about their health while they are enrolled in this study. They may choose to withdraw at any time. Subjects will be advised that data collected in this study will be provided to the Sponsor, and may be reported to regulatory authorities or published in scientific journals. In any of these events, the subjects' identities will not be revealed.

10.2.1 Inclusion Criteria:

Subjects meeting all of the following criteria will be considered for enrollment in the study:

1. Egyptian male and female patients aged between 18-65 years' old
2. Subjects having pelvi-abdominal infections such as and not limited to: Ulcerative colitis, Diverticulitis, Cholecystitis, and PID (e.g oophoritis and salpingo-oophoritis).
3. Subjects during post-operative period for pelvi-abdominal surgery and following IV medication with Metronidazole injection plus third generation cephalosporin.
4. Subjects who are willing to sign Informed Consent Form (ICF) and ready to comply with the protocol for the duration of the study

10.2.2 Exclusion Criteria:

Subjects presenting with any of the following will not be included in the study:

1. Subjects with a history of hypersensitivity to any of the active ingredients of the treatments used
2. Subjects who are receiving or received any other antibiotics during the previous two weeks, rather than IV treatment in the first post-operative 48 hours, mentioned in the protocol (Metronidazole injection plus third generation cephalosporin)
3. Subjects with Pelvi-abdominal infection and performed surgery after failure of oral antibiotics.
4. Subjects having surgeries such as colorectal surgeries, appendectomy and ovarian cystectomy
5. Subjects with any medical condition requiring the usage of the following medications:

a. Drugs that induce microsomal liver enzymes, such as Phenytoin or Phenobarbital, may accelerate the elimination of metronidazole
b. Drugs that decrease microsomal liver enzymes activity, such as cetrimide, may prolong the half-life and decrease plasma clearance of metronidazole.
c. Administration of theophylline in combination with Ciprofloxacin may lead to cardiac arrest, seizures, status epilepticus, and respiratory failure
d. Administration of corticosteroids in combination with Ciprofloxacin may lead to tendinitis
e. Antacids containing magnesium and aluminum, supplements and other products containing calcium, iron or zinc as they reduce the effect of Ciprofloxacin.
f. Tizanidine because this may cause low blood pressure and sleepiness

6. Subjects with uncontrolled diabetes mellitus; FBG > 200 mg/ml
7. Subjects with renal impairment (S. Creatinine > 1.5 mg/dL)
8. Subjects with hepatic impairment (Child-Pugh Score B-C)
9. Subjects with liver enzymes (SGOT, SGPT) > 2 times Normal range.
10. Pregnant or breast feeding women

10.2.3 Discontinuation/Withdrawal of participants from the study:

Each participant has the right to withdraw from the study at any time.
In addition, the investigator may discontinue a participant from the study at any time if the investigator considers it necessary for any reason including:

1. Ineligibility (either arising during the study or retrospective having been overlooked at screening)
2. Significant protocol deviation
3. Significant non-compliance with treatment regimen or study requirements
4. Disease progressions which requires discontinuation of the study medication or results in inability to continue to comply with study procedures.
5. Consent withdrawn by subject.
6. Lost to follow up
7. SAE or death
8. If a female subject becomes pregnant
9. Subjects which have Cholecystitis and it will be operated upon.

The reason for withdrawal will be recorded in the CRF. If the participant is withdrawn due to an adverse event, the investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilized.

10.2.4 Assessments to be done:

1- Screening Visit Assessments:

- The enrollment period will be 12 months including the screening visit. Screening assessments will be completed and treatment will be initiated within visit 1.
- During this visit, patients will be screened for fulfillment of the inclusion and exclusion criteria and written informed consent will be obtained.
- Screening assessments will include physical examination, medical history, patient demographics, vital signs, concomitant medications, safety laboratory tests

(including Fasting Blood Sugar (FBS), Total leukocyte count, Liver enzymes (SGOT & SGPT), Total Bilirubin and S. Creatinine), Child-Pugh Score (for hepatic impairment) and, β-HCG (for females of child bearing potential only) and pelvi-abdominal Ultrasound & others.

- Presence of any signs/symptoms of post-operative wound infection such as redness, fever or wound discharge will be recorded (in case of post-operative subjects)

2- Follow-up 1 Visit:(Day 8):

- On-treatment assessments include physical examination, vital signs, AEs, SAEs, concomitant medication and study drug dosing compliance
- Days for complete healing will be checked
- Complete resolution, improvement, failure or relapse of Pelvi- abdominal infection
- Presence of any signs/symptoms of post-operative wound infection such as redness, fever or wound discharge will be recorded (in case of post-operative subjects)

3- Follow-up 2 Visit & End of study visit (Day 15):

- Assessments include physical examination for vital signs, AEs, SAEs, concomitant medication, and study drug dosing compliance
- Pelvi-abdominal Ultrasound and others will be done, if needed upon Physician's decision.
- Days for complete healing will be checked
- Complete resolution, improvement, failure or relapse of Pelvi- abdominal infection
- Presence of any signs/symptoms of post-operative wound infection such as redness, fever or wound discharge will be recorded (in case of post-operative subjects)
- Safety laboratory tests (including Total Leucocytic count, Liver enzymes (SGOT & SGPT), Total Bilirubin and S. Creatinine)
- The End of Study Form must be completed.

10.3 Variables:

10.3.1 Primary Endpoints:

1- Primary Safety:

Incidence of serious/non-serious adverse events

2- Primary Efficacy:

- Complete resolution for pelvi-abdominal infection based on pelvi-abdominal ultrasound and others and/or clinical response
- Complete healing of post-operative wounds

10.3.2 Secondary Endpoints:

1- Secondary Safety:

- Presence of any signs/symptoms of post-operative wound infection such as redness, fever or wound discharge.
- Change in Total leukocytes count and Liver enzymes (SGOT, SGPT), between baseline (visit 1) to End of study visit (Follow up 2 visit)

-

2- *Secondary Efficacy:*

- Describe complete resolution, improvement, failure or relapse of pelvi- abdominal infection based on pelvi-abdominal ultrasound and others and or clinical response.
- Days for complete healing of post-operative wounds after 8 days of treatment (Follow-up 1 V) & 15 days of treatment (End of study visit) between the 2 groups

10.4 Data Sources:

All visits assessments will be kept in the source files for each patient and in CRF, which will be verified by the CRA responsible.

10.5 Study Size

Subjects having pelvi-abdominal infection, in post-operative period of pelvi-abdominal surgeries or acute conditions will be selected from the surgical department in Menoufia University Hospital and some subjects might be referred from other departments in Menoufia University Hospital such as and not limited to; the department of Gynecology and Obstetrics. Patients will be asked to participate in the study and sign the informed consent, then screening for inclusion and exclusion criteria will be done and recorded in the patient's medical records (either enrolled or screening failure).

10.5.1 Determination of Sample Size

As the primary objective is to assess the safety of oral Ciprodiazole ® tablets (Ciprofolxacin /Metronidazole) versus currently used Ciprofloxacin Tablets & Metronidazole tablets following IV antibiotics in post-operative period, for pelvi-abdominal surgeries, and based on the previous study "Comparison of Intravenous/Oral Ciprofloxacin Plus Metronidazole Versus Piperacillin / Tazobactam in the Treatment of Complicated Intra-abdominal Infections".[15] Overall clinical resolution rates were statistically superior for CIP+MET (74%) compared with PIP/TAZO (63%). Mean length of stay was 14 days for CIP1MET and 17 days for PIP/TAZO patients.

So, the following parameters are used to calculate the expected sample of the study:

- Design: non-inferiority
- Sample Size = 312 Subjects (1:1)
- Ciprodiazole Sample Size (Experimental group) = 156 subjects
- Current used regimen Sample Size (Control group) = 156 subjects
- Confidence level 95% (α error = 5%)
- Power = 80%
- Non-Inferiority margin = 2%

10.5.2 Sample Size & Treatment Groups:

Total of 312 Egyptian patients who have pelvi-abdominal infection or started IV antibiotics in post-operative period, for pelvi-abdominal surgeries will be enrolled in the study and randomized, using a computer system, with a ratio of 1:1, into two categories as follows:

1. Group will receive Ciprodiazole ® tablets; 156 patients
2. Group will receive Ciprofloxacin Tablets & Metronidazole tablets; 156 patients

10.5.3 Randomization:

Subjects will be randomized into the two treatment groups with a balanced ratio of 1:1. Randomization by block Computer-generated randomization lists will be established by Data Management department (DM) of CRO (Nagy Research). The number of patients of the two treatment groups will be balanced (ratio 1:1). (156 Ciprodiazole ®: 156 Ciprofloxacin Tablets & Metronidazole tablets).

A document describing the procedure of constitution of the randomization lists will be stored confidentially at Nagy Research CRO

Block size: 2, 4

The Randomization list will be done using website:
(https://www.sealedenvelope.com/simple-randomiser/v1/lists)

10.6 Data Management

Data will be entered into a computer database with independent double data entry and will be validated with computer checks and manual review against source files. The patient's data will remain confidential, since only the patients' initials are on the CRFs. Queries will be sent to the investigators using data clarification forms, and resolved by the investigators who will sign and date the respective data clarification forms. Corresponding changes in the database will be made, documented, and independently verified. Subjects who drop out will fill the reason for premature end of the study and will be documented.

10.7 Data Analysis

10.7.1 Analysis populations

Analysis of all efficacy variables will be performed only for patients who completed the study without protocol violation (as per protocol).
Analysis of all safety variables will be performed for all patients (intent-to-treat population), who received even 1 dose of the treatment; either Ciprodiazole ® tablets or currently used Ciprofloxacin Tablets & Metronidazole tablets.

10.7.2 Statistical methods

This section provides specifications for preparation of final Statistical Analysis Plan (SAP), which will be issued prior to database lock. Any differences compared to this statistical section should be identified and documented in final SAP. Analysis will be done using SPSS version 21.

10.7.3 Analysis variables

Descriptive Analysis:

- Descriptive analysis of the collected data. All enrolled patients will be included in the safety analysis.
- All quantitative primary and secondary end point variables will be described
- Data from primary and secondary endpoints will be summarized using appropriate summary statistics i.e. n (number of subjects), mean, Standard Deviation (SD), median and range.

Comparative Analysis:

- All tests will be performed on the 5% level of significance.
- Chi² test for unpaired categorical variables.
- Paired t-test to estimate the change in numerical variables throughout the study visits.
- Student t-test to estimate the comparison between the subgroups for the numerical variables.
- *P*-values less than 0.05 will be considered statistically significant

10.7.4 Main criteria

- To compare safety of oral Ciprodiazole ® tablets (Ciprofolxacin/Metronidazole) versus currently used Ciprofloxacin Tablets & Metronidazole tablets in pelvi-abdominal infections, either non-operative or post-operative following IV antibiotics.
- To compare efficacy of oral Ciprodiazole ® tablets (Ciprofolxacin/Metronidazole) versus currently used Ciprofloxacin Tablets & Metronidazole tablets in pelvi-abdominal infections, either non-operative or post-operative following IV antibiotics.

10.7.5 Other criteria

- To describe presence of any signs/symptoms of post-operative wound infection such as redness, fever or wound discharge.
- To describe presence of undesirable effects on total leukocyte count and liver enzymes (SGOT & SGPT) between baseline (visit 1) to End of study visit (Follow up 2 V)
- To compare the complete resolution, improvement, failure or relapse of Pelvi- abdominal infection between ciprodiazole® versus combined treatment, based on pelvi-abdominal ultrasound and others
- To compare the number of days for complete healing of post-operative wounds between ciprodiazole® versus combined treatment

10.7.6 Primary Safety analysis

A. Number of participants experiencing Serious Adverse Events (SAEs). [Time Frame: visit 1 to End of study visit].

- Frequency distribution (number & percent) of occurrence of SAEs necessitating a change or discontinuation of treatment. Chi² test will be used to determine *p*-value and significance between the 2 groups.

- Frequency distribution (number & percent) of type and severity of SAEs. Chi² test will be used to determine *p*-value and significance between the 2 groups.

B. Number of participants experiencing Adverse Events (AEs) leading to permanent discontinuation of the study drug. [Time Frame: visit 1 to End of study visit].

- Frequency distribution (number & percent) of causes of treatment discontinuations. Chi² test will be used to determine *p*-value and significance between the 2 groups.

- Frequency distribution (number & percent) of occurrence of AEs necessitating a change or discontinuation of treatment. Chi² test will be used to determine *p*-value and significance between the 2 groups.

- Frequency distribution (number & percent) of type and severity of AEs. Chi² test will be used to determine *p*-value and significance between the 2 groups.

10.7.7 Primary Efficacy analysis:

A. Complete resolution for Pelvi- abdominal infection based on pelvi-abdominal Ultrasound

- Frequency distribution (number & percent) of complete resolution for pelvi-abdominal infection. Chi² test will be used to determine *p*-value and significance between the 2 groups.

B. Complete healing of the post-operative wounds [Time Frame: Follow-up 1 V to End of study visit].

- Frequency distribution (number & percent) of complete healing of the post-operative wounds. Chi² test will be used to determine *p*-value and significance between the 2 groups.

- Frequency distribution (number & percent) of incomplete healing of the post-operative wounds. Chi² test will be used to determine *p*-value and significance between the 2 groups.

- Frequency distribution (number & percent) of no healing of the post-operative wounds. Chi² test will be used to determine *p*-value and significance between the 2 groups.

10.7.8 Secondary Safety analysis:

A. Presence of any signs/symptoms of post-operative wound infection such as redness, fever or wound discharge [Time Frame: visit 1 to End of study visit].

Frequency distribution (number & percent) of presence of any signs/symptoms of post-operative wound infection such as redness, fever or wound discharge. Chi² test will be used to determine *p*-value and significance between the 2 groups.

B. Change in Total leukocytes count between baseline (visit 1) to End of study visit

Descriptive analysis (mean, Standard Deviation, Median, Interquartile Range, Minimum and Maximum) of total leucocyte will be from baseline (visit 1) to End of study visit. Percent change will be calculated between baseline to End of study. Paired t-test will be used to determine *p*-value and significance between baseline and at the end of the study. Unpaired t-test will be used to determine the *p*-value and significance between Changes in total leucocyte between 2 groups.

C. Change in Liver enzymes (SGOT) between baseline (visit 1) to End of study visit

Descriptive analysis (mean, Standard Deviation, Median, Interquartile Range, Minimum and Maximum) of Liver enzymes (SGOT) will be from baseline (visit 1) to End of study visit. Percent change will be calculated between baseline to End of study. Paired t-test will be used to determine *p*-value and significance between baseline and at the end of the study. Unpaired t-test will be used to determine the *p*-value and significance between Changes in Liver enzymes (SGOT) between 2 groups.

D. Change in Liver enzymes (SGPT) between baseline (visit 1) to End of study visit

Descriptive analysis (mean, Standard Deviation, Median, Interquartile Range, Minimum and Maximum) of Liver enzymes (SGPT)will be from baseline (visit 1) to End of study visit. Percent change will be calculated between baseline to End of study. Paired t-test will be used to determine *p*-value and significance between baseline and at the end of the study. Unpaired t-test will be used to determine the *p*-value and significance between Changes in Liver enzymes (SGPT) between 2 groups.

10.7.9 Secondary Efficacy analysis:

A. Complete resolution, improvement, failure or relapse of Pelvi- abdominal infection

- Frequency distribution (number & percent) of complete resolution, improvement, failure or relapse for Pelvi- abdominal infection. Chi² test will be used to determine *p*-value and significance between the 2 groups.

- Frequency distribution (number & percent) of improvement for Pelvi- abdominal infection. Chi² test will be used to determine *p*-value and significance between the 2 groups.

- Frequency distribution (number & percent) of failure for Pelvi- abdominal infection. Chi² test will be used to determine *p*-value and significance between the 2 groups.

- Frequency distribution (number & percent) of relapse for Pelvi- abdominal infection. Chi² test will be used to determine *p*-value and significance between the 2 groups.

B. Days for complete healing of post-operative wounds after 8 days of treatment (Follow up 1 visit) & 15 days of treatment (Follow up 2 visit or End of study visit)

Descriptive analysis (mean, Standard Deviation, Median, Interquartile Range, Minimum and Maximum) of days for complete healing versus combined treatment will be after 8 days of treatment (Follow-up 1 V) & 15 days of treatment (End of study visit). Percent change will be calculated between baseline to End of study. Paired t-test will be used to determine *p*-value and significance between baseline and at the end of the study. Unpaired t-test will be used to determine the *p*-value and significance between Changes in complete healing between 2 groups.

10.7.10 Interim analysis

Optional

10.7 Quality Control

10.8.1 Quality Assurance

To ensure uniformity of study procedures across centers, the protocol, case report form, and safety reporting procedures will be reviewed with the investigators and his/her personnel responsible for the conduct of the study. Adherence to the protocol and verification of source data will be achieved through monitoring visits to the center. During the course of study monitoring, the entire study documentation will be checked for completeness and plausibility by the responsible CRA. Once the CRF is completed and signed, the CRA takes the data management copy and the data is entered into the database for analysis. CRFs will be kept in secure locked place or lockers.

10.8 Limitation of the research methods

Any issues relating to confounding, bias, generalizability, and random error are considered as a limitation to the study results. This study is randomized, open label, controlled study, which avoids bias from the physicians, patients or biostatistician. Also, the study results are taken upon source document verification with the CRF in order to ensure the quality and non-bias of the data.

11 Protection of Human Subjects

This study will be conducted according to Good Clinical Practice (ICH-GCP) and in accordance with the Declaration of Helsinki as adopted by the 18th World Medical Assembly 1964 and subsequent amendments: Tokyo (1975), Venice (1983), Hong Kong (1989), Somerset West, Republic of South Africa (1996) and Edinburgh (2000).

This study will be conducted in compliance to Good Clinical Practice (ICH-GCP) and in accordance with the Declaration of Helsinki, with a qualified principle investigator.

Before the start of the study, subjects who appear suitable for inclusion in the study will be informed, as outlined in the protocol, about the objective, nature, scope, and potential benefits and risks of the study and any discomfort it may entail. The subject will be allowed sufficient time to reach a decision. The subject's consent will be documented on the form provided, which will be retained by the investigator; a copy of the informed consent declaration will be given to the subject to retain. Under the circumstances where signed informed consent is difficult to obtain from subjects due to illiteracy, witness should sign that the subject has been informed about all details of informed consent. The informed consent will be also signed and dated by the person who obtained the informed consent and signed/finger printed by the study participant, or his legal representative.
The subject will be assured that all personal data would be treated in strict confidence. In the event that information of relevance to the subject became available during the study, this will be communicated to the subject. The subject has the right to withdraw the informed consent at any time. No study-specific investigations would be performed and no study-

specific medication will be administered before informed consent is obtained .Case Report Forms will be provided for each subject's data to be recorded.

12 Study Procedures:

12.1 Informed consent:

- The investigator must provide the patient with relevant, comprehensive, verbal and written information regarding the objectives and procedures of the study as well as the possible risks involved, as per ICH-GCP guidelines.
- The patient should have enough time and opportunity to inquire about study details. All their questions should be answered in satisfying manner.
- The patient must be informed about their right to withdraw from the study at any time, without having to give a reason.
- Signed and dated informed consent must be obtained from all patients and in case of an illiterate patient, the patient will finger print with a witness who will sign and date, before undertaking any study related procedures, without any pressure or unduly influence from the treating doctor.

12.2 Patient Enrollment

After signing the informed consent form, each potential subject will be screened for eligibility based on the inclusion and exclusion criteria specified. Randomization will be done.

All visits will occur as closely as possible to the scheduled visit dates with window of 3 days. In case of a premature discontinuation of the study, the subject, will be, if possible called in for a last visit. Even if the subject would not be able to attend, the 'End of Study' forms will be completed .

12.3 12.3 Schedule of visits

Table 1: Schedule of Visits

Observation	**Visit 1 (Screening & treatment)**	**(Follow-up 1 V)**	**(Follow-up 2 V) End of Study**
Time lines	**Day 0**	**Day 8**	**Day 15**
Informed consent document signed	X		
Review Inclusion/Exclusion criteria	X		
Patient Demographics	X		
Significant medical history and current disease status	X		
Physical examination	X	X	X
Vital Signs	X	X	X
Child-Pugh Score	X		
Concomitant medications	X	X	X
Safety Laboratory Tests:			
FBS	X		
Total Leucocytic count	X		X
SGOT (ALT)	X		X
SGPT (AST)	X		X
Total Bilirubin	X		X
S. Creatinine	X		X
Serum β-HCG: (for females in childbearing period)	X		
Pelvi-abdominal Ultrasound & others (Optional)	X		X
Study Drug Dispensed	X	X	
Drug Accountability		X	X

Observation	Visit 1 (Screening & treatment)	(Follow-up 1 V)	(Follow-up 2 V) End of Study
Time lines	**Day 0**	**Day 8**	**Day 15**
Presence of any signs/symptoms of post-operative wound infection such as redness, fever or wound discharge. (in case of post-operative subjects)	X	X	X
Days for complete healing		X	X
Complete resolution, improvement, failure or relapse of pelvi - abdominal infection		X	X
AE		X	X
SAE		X	X
Study Completion Form			X

The subsequent visits will occur as follows :

- **Visit 1 (Screening & treatment initiation Visit):** Day 0
- **Follow-up V1:** Day 8 (+/-) 3 days
- **Follow-up V2 & End of Study Visit:** Day 15 (+/-) 3 days

12.3.1 Visit 1 (Screening & treatment initiation):

- During this visit, subjects will be informed about the study. If they are willing to participate in the study, they will sign the written ICF. A copy of the signed ICF will be given to the subject. In addition, the subjects will be evaluated for study eligibility according to the inclusion and exclusion criteria.
- Screening Assessments will include: physical examination, vital signs, demographic data (Age & Gender), medical history and concomitant medications.
- Presence of any signs/symptoms of post-operative wound infection such as redness, fever or wound discharge will be recorded (in case of post-operative subjects)
- Child-Pugh Score will be calculated for liver impairment and pelvi-abdominal Ultrasound and others will be done
- Lab results will be checked for: (Fasting Blood Sugar (FBS), Total leukocytes count, liver enzymes (SGOT & SGPT), Total Bilirubin and S. Creatinine), and Serum β-HCG for females of child bearing potential only
- The Investigator will keep a log of all subjects, who will sign the ICF. Even if the subject would not pass the screening, his/her signed consent form will be retained

in the Investigator file and will be considered as screening failure. The reason(s) for screen failure will be recorded in the screen failure form in the screening log.

- All data related to screening visit must be reviewed (signed and dated) by the Investigator to ensure that the subject will be eligible for the study, before dispensing the study drug.
- Randomization will be done and subjects will be administered the study products; either Ciprodiazole® tablets or Ciprofloxacin Tablets & Metronidazole tablets.
- Study products sufficient for the next 7 days will be supplied; either Ciprodiazole® tablets or Ciprofloxacin Tablets & Metronidazole tablets, and storage conditions will be explained. Study products supplied will be recorded.
- Subjects will be asked to come after 7 days of treatment and bring the empty blisters of medication received, with window of 3 days.

In case of any premature discontinuation of the study, the subject will be, if possible, called in for a last visit. Even if the subject was not able to attend the last visit, the End of Study Form must be completed.

Child-Pugh Score will be recorded, as follows:

The score employs five clinical measures of liver disease. Each measure is scored 1-3, with 3 indicating most severe derangement. [20]

Table 2: Child-Pugh Score

Measure	1 point	2 points	3 points
Total bilirubin, µmol/l (mg/dl)	<34 (<2)	34-50 (2-3)	>50 (>3)
Serum albumin, g/dl	>3.5	2.8-3.5	<2.8
Prothrombin time, prolongation (secs)	<4.0	4.0-6.0	> 6.0
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

In primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC), the bilirubin references are changed to reflect the fact that these diseases feature high conjugated bilirubin levels. The upper limit for 1 point is 68 µmol/l (4 mg/dl) and the upper limit for 2 points is 170 µmol/l (10 mg/dl).

Chronic liver disease is classified into Child-Pugh class A to C, employing the added score from above.

Table 3: Child-Pugh Classes

Points	Class
5-6	A
7-9	B
10-15	C

The Investigator will keep a log of all subjects who will sign the consent form. Even if the subject would not pass the screening, his/her signed consent form will be retained in the Investigator file.

12.3.2 Follow-up 1 Visit (Day 8)

It could the end of treatment for some subjects.

The following procedures will be done this visit, and all relevant information will be recorded in the source document and forms:

- Subjects will undergo thorough general physical examination and Vital signs
- Presence of any signs/symptoms of post-operative wound infection such as redness, fever or wound discharge will be recorded (in case of post-operative subjects)
- Any changes in concomitant medication, illness and treatment will be recorded.
- Checking if any AE or SAEs happened and recording them in their separate forms.
- Days for complete healing will be checked, if happened.
- Complete resolution, improvement, failure or, relapse of Pelvi- abdominal infection will be recorded
- Subjects will be asked to come after 15 days of the treatment (Day 15) for follow up, with window of 3 days
- In case of any premature discontinuation of the study, the subject will be, if possible, called in for a last visit. Even if the subject was not able to attend the last visit, the End of Study Form must be completed.
- In case of complete resolution, end of the study lab testing will be asked and recorded and End of the study Form will be completed

12.3.3 Follow-up 2 Visit & End of Study Visit (Day 15):

It is the end of study visit for subjects.

The following procedures will be done during this visit, and all relevant information will be recorded in the source document and forms:

- Subjects will undergo thorough general physical examination and Vital signs
- Presence of any signs/symptoms of post-operative wound infection such as redness, fever or wound discharge will be recorded (in case of post- operative subjects)
- Any changes in concomitant medication, illness and treatment will be recorded.
- Checking if any AE or SAEs happened and recording them in their separate forms. Days for complete healing will be checked.
- Complete resolution, improvement, failure or, relapse of Pelvi- abdominal infection will be recorded
- Lab results will be checked for: S. Creatinine, Total leukocytes count, Liver enzymes (SGOT, SGPT), and total bilirubin
- Pelvi-abdominal Ultrasound and others will be done, if needed.
- The End of Study Form must be completed.

13 Management & Reporting of Adverse Events

The physician is responsible for the safety of the patient. The sponsor is responsible for the safety of his product and for reporting safety issues to the regulatory bodies according to appropriate regulations. In order for all parties to comply with their responsibilities, it is important that the physician documents and processes quality and safety issues in the following manner.

13.1 Adverse Events (AEs):

An AE is any undesirable medical event occurring to a subject in a clinical trial, whether or not considered related to the trial product(s). This includes events not seen at baseline or worsened if present at baseline. The following will not be recorded as AEs, if recorded at screening visit: Pre-existing conditions found as a result of screening procedures.

Assessment of Intensity/Severity:

The intensity or severity of an AE is defined as follows :

- Mild: Transient symptoms, no interference with the subject's daily activities.
- Moderate: Marked symptoms, moderate interference with the subject's daily activities.
- Severe: Considerable interference with the subject's daily activities, unacceptable

Assessment of Causality (as per WHO-UMC)

The **relationship** of each AE to the study drug where there is a demonstrable cause-effect association between two events, assessed by the investigator:

Causality Term	Assessment of Causality
Certain	•Event or laboratory test abnormality, with plausible time relationship to drug intake •Cannot be explained by disease or other drugs •Response to withdrawal plausible (pharmacologically, pathologically) •Event definitive pharmacologically or phenomenological (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) • Re-challenge satisfactory, if necessary
Probable /Likely	•Event or laboratory test abnormality, with reasonable time relationship to drug intake •Unlikely to be attributed to disease or other drugs •Response to withdrawal clinically reasonable • Re-challenge not required
Possible	•Event or laboratory test abnormality, with reasonable time relationship to drug intake •Could also be explained by disease or other drugs •Information on drug withdrawal may be lacking or unclear
Unlikely	•Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) •Disease or other drugs provide plausible explanations
Conditional/ Unclassified	•Event or laboratory test abnormality •More data for proper assessment needed, or additional data under examination
Un-assessable /Unclassifiable	•Report suggesting an adverse reaction •Cannot be judged because information is insufficient or contradictory •Data cannot be supplemented or verified

Outcome categories

The outcome of each AE is recorded on the CRF, according to the following definitions :

- Death Related to Adverse Event: if the termination of life as a result of an adverse event.
- Not Recovered or Not Resolved: to indicate that the event has not improved or recuperated.
- Recovered or Resolved: if the event has improved or recuperated.
- Recovered or Resolved with Sequelae: if the subject recuperated but retained pathological conditions resulting from the prior disease or injury.
- Recovering or Resolving: if the event is improving but has not yet fully recovered
- Unknown: if the outcome was not known, not observed or not recorded

Clinical Laboratory Adverse Events (CLAEs)

A Clinical laboratory AE is any abnormal clinical laboratory value that suggests a disease and/or organ toxicity and is of a severity, which requires active management i.e. change of dose, discontinuation of drug, more frequent follow-up or diagnostic investigation.

13.2 Serious Adverse Events (SAEs)

A SAE is any adverse drug experience that at any dose results in any of the following outcomes :

- Death
- A life-threatening experience
- Subject hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- Congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious drug experience when, based upon appropriate medical judgment, they jeopardize the health of the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

In case of unexpected pregnancy for the study subject or study subject's spouse, pregnancy reporting will be completed; for the outcome of the pregnancy and if there are any congenital anomaly.

Non-serious Adverse Event: A non-serious adverse event is any AE, which does not fulfill the definition of a SAE .

Collection, Recording, and Reporting of Adverse Events :

- Any information regarding any adverse event will be collected and reported from the first study related activity till the end of the study and post-treatment follow-up period .
- At each contact, the subject will be asked about adverse events.
- All adverse events, either observed by the Investigator or reported by the subject, will be recorded by Investigator and evaluated .

Adverse events will be assessed at each visit. The subject will be asked about the adverse events. Adverse events will be recorded both in the source document and the CRF. The Investigator needs to record the diagnosis, if available. If no diagnosis will be available, the Investigator records each sign and symptom as an individual adverse event. The patient is given the investigator's number to contact him 24/7 in case of any adverse event.

All adverse events will be collected and recorded by the Investigator on the Adverse Event Form of the CRF and to the monitor for safety reporting. One single Adverse Event Form must be used per adverse event from start to resolution of the event. CIOMS form will be completed for all serious adverse events & reported to the Egyptian Pharmacovigilance Center (EPVC) as per the GVP timelines (During 15 calendar days for SAEs & 90 calendar days for non-serious AEs). Follow-up of all adverse events till resolution or stabilization. The reporting of SAE to the national medicines regulatory authority is a must, within 24 hours of PI notification, as per the IRB/EC of site and RHD of Egyptian MOH.

During subject's participation in the study, the Investigator/Institution will ensure that adequate medical care will be provided to the subject for any adverse event including clinically significant laboratory values related to the study. When the Investigator becomes aware of the adverse event, he/she will inform the subject and does the necessary follow-up.
Only unresolved AEs will be followed up actively until the AE has resolved or stabilized. No active follow-up with the subjects will be made during this period for occurrence of new adverse events.

14 Plans for disseminating & communicating study results

14.1 Progress Report

Timely progress reports will be submitted according to the national medicines regulatory authority. The content of the progress report includes all the available data that are judged relevant to the progress of the study.

14.2 Final Study Report

The final study report will be submitted as soon as possible within 3 months of database lock. If the study is discontinued for any reason; a final report will be submitted and the reasons for terminating will be provided. The title, version and date of the protocol and author will be written in the title page.
The final study report will follow Arab GVP content & include but not limited to:
An abstract of the study, rationale and background, research methods, demographic, baseline characteristics, safety parameters will be analyzed for the total population of all enrolled (randomized) subjects. Efficacy analysis will be performed for the 'Per Protocol populations only. ITT patients will be analyzed for safety in the results section; results and limitations will be discussed in the discussion section of the report.
Population is defined as follows :

- Intention to Treat (ITT): all enrolled subjects with at least one baseline and one post-baseline visit.
- Per Protocol (PP): all enrolled subjects who completed according to the protocol with no protocol deviations.

Continuous variables will be summarized using mean, standard deviation, median, and range (minimum and maximum), while categorical variables will be summarized using proportions (counts and percentages) .
Data on subject disposition (number of subjects enrolled, number of drop-outs, and reasons for drop-out), demographics (gender, age, weight, height), and other baseline characteristics (physical examination results, vital signs, and laboratory assessments) will be summarized.
All biostatical results and analysis will be done as per endpoints as per protocol, as per section 10.7.
Additionally, for each treatment, the incidences of all treatment emergent AEs will be tabulated by body system and preferred term (to which each AE will be mapped, using World Health Organization Adverse Reaction Terminology (WHO-ART), version 1998/04). Other information regarding AEs, such as intensity, seriousness, causality, and discontinuations due to AEs, will be also tabulated by treatment. AEs that are reported

more than once by a subject will be counted only once for that subject at the maximum intensity.
Concomitant medications will be tabulated by generic drug names, based on World Health Organization Drug Dictionary (WHO-DD), version 1998/04.

15 Confidentiality and publication

Patient names must be kept confidential and should not appear on any CRF page or study specific documents.
The sponsor and health authorities are obligated to respect medical secrecy and to refrain from divulging any personal patient information

15.1 Use of information

The study data are the property of the sponsor (Minapharm Pharmaceuticals). The investigator and any of the research staff shall obtain written approval from the sponsor prior to the publication/communication of the results of any work carried out during or in relation to the study

16 Archiving

The investigators should retain all essential study-related documents e.g. signed protocol, investigator's brochure, CRFs, medical records, laboratory reports, etc. in accordance with the applicable regulatory requirements of his/her country.
The study-related documents should be kept together in the investigator site file provided to the investigator by the sponsor for minimum 5 years.

17 Responsibility of Participants

17.1 Responsibility of Investigators

The investigators will conduct the study in accordance with ICH-E6, all applicable laws in the country where the study is conducted and in accordance with this study protocol
The responsibilities of the investigator are summarized below but not limited to:

1. Patient's information and consent
2. Information on the overall results of the study
3. Information to other practitioners
4. Adverse Events recording
5. Data Recording in paper CRF
6. Record Retention
7. Use of study-related information
8. Medicinal Product
9. Quality Control
10. Study Discontinuation
11. Delegation of investigator duties
12. Study Agreement Discontinuation
13. Collect unused/returned drug from patients

14. Return collected unused/returned drugs to CRO; on behalf of Minapharm

17.2 Responsibility of CRO:

1. Design and write the protocol.
2. Design the statistical section of the protocol
3. Design CRFs
4. Design informed consent
5. Collect regulatory documents (EC of site and RHD of MOH)
6. Develop investigator agreement template
7. Prepare investigator's signatures on participation in study
8. Prepare Ethics Committee/ RHD of MOH file
9. Ethics Committee followed by RHD of MOH submissions and collecting approvals.
10. Follow up reports to Ethics Committee / RHD of MOH
11. Design & distribute study site staff manual
12. Train study site staff for GCP, CRF completion and safety notification: PI, co-investigators & rest of site staff
13. Conduct initiation visits
14. Set up trial master file (TMF) and Investigator Site File (ISF) for Principle Investigators
15. Design study tracking system
16. Randomization list
17. Provide pharmacy briefing (temperature & etc.,)
18. Conduct drug accountability
19. Collect unused/returned drug from investigators
20. Destroy unused/returned drug
21. Conduct SIV, Follow-Up Monitoring visits and Close out visits.
22. Provide site management
23. Resolve CRF queries
24. Provide project management services
25. Revise SAE reports and send all AE cases (serious & non-serious) to EC & regulatory (RHD of MOH and EPVC)
26. Prepare and submit regular interim report to EC of site and RHD of MOH including safety reporting of all adverse events whether serious or non-serious.
27. Design/build database

28. Generate queries
29. Lock database
30. Ship project-related documents to Sponsor
31. Create statistical analysis plan
32. Write statistical report
33. Write interim and final clinical study report
34. Write publication manuscript
35. Assist on publication of paper in medical journal

17.3 Responsibility of the Monitor

The responsibilities of the study monitor are defined in ICH-E6, Chapter 5. The monitor, who is mandated by the sponsor, must ensure that the study is conducted in accordance with GCP guidelines and all applicable local laws and that the rights, the security and well-being of the patients are respected.
Responsibilities include:

1. Communication
2. Training
3. Compliance
4. Source Data Verification
5. IP (in association with the sponsor).

17.4 Responsibility of the Sponsor

The sponsor; the pharmaceutical company (MINAPHARM) which is responsible and initiates the clinical investigation.

Responsibilities include:

1. Selecting qualified investigators.
2. Determine investigator budget.
3. Providing the investigators with the information they need to conduct an investigation properly.
4. Identify the laboratory and other investigation centers
5. Prepare Contract for laboratory
6. Contracting an insurance company for the clinical study
7. Ensuring proper monitoring of the investigation.
8. Ensuring that the investigation is conducted in accordance with the general investigational plan and protocol.
9. Shipping medicinal new drugs only to sites which are participating in the investigation.
10. Giving each participating clinical investigator/ site an investigator brochure.

11. Reviewing and evaluating the evidence related to the safety and effectiveness of the drug as it is obtained from the investigator.
12. If determining that its medicinal drug presents an unreasonable and significant risk to subjects, the sponsor will discontinue those investigations that present the risk, notify the medicine authorities, all institutional review boards and all investigators who have at any time participated in the investigation of the discontinuance.
13. Reporting all adverse events to EPVC (Egyptian Pharmaco Vigilance Center) as per the GVP timelines

17.5 Responsibility of the Data Manager

The primary responsibility of data manager is to enter data from case report forms (CRFs) to computed database. The data manager is responsible for collecting all source documentation and worksheets prepared by all members of the research team and then transcribing the data on to the appropriate collection tool for submission to the sponsor.

Specific responsibilities include but are not limited to the following:

- Source document archiving after receiving from CRA.
- File and pull study records
- Case report form design, design CRF completion guidelines and its entry by assigned personnel
- Review data for accuracy and completeness
- Clarify data with research staff as necessary
- Enter data into the computer
- Correct/revise data as appropriate
- Maintain back-up system for computerized data

18 Audit and Inspection

An audit/inspection may be carried out by qualified sponsor staff, by subcontracted auditors or by representatives of national or foreign health authorities to ensure that the study is conducted as per protocol and in accordance with regulatory requirements, and to ensure the validity of the data.
Participation in this study implies acceptance to cooperate in any potential audit/inspection. Audit/inspection may take place after the end of the study.

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