STUDY PROTOCOL

STUDY ON THE SAFETY OF ADMINISTERING ISONIAZID TO SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS TO PREVENT TUBERCULOSIS

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PADJADJARAN UNIVERSITY

2024

STUDY PROTOCOL

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Aim

This study aims to prove that the administration of Isoniazid (INH) in the prevention of Tuberculosis (TB) in patients with Systemic Lupus Erythematosus (SLE) is safe against liver toxicity and disease recurrence.

Research Design

An open-label, randomized, controlled, prospective cohort study evaluating two groups of SLE patients, those receiving INH and pyridoxine for nine months and those not receiving both drugs. Signs and symptoms of drug-induced hepatotoxicity and degree of SLE disease activity were assessed monthly for the first three months (months 1/2, 1, 2, and 3), and then continued every three months for up to one year (months 6, 9, and 12).

Introduction

Systemic Lupus Erythematosus (SLE) is a highly complex chronic autoimmune disease that affects multiple organs.[1] The course of the disease is influenced by many things, one of which is infection.[2] SLE patients are more susceptible to infections, due to their disease activity as well as the use of immunosuppressant drugs and glucocorticoids.[3] One of the infections that mainly affects SLE patients is Tuberculosis (TB) infection,[4] especially patients living in Asian areas that are endemic to TB.[5]

TB infection increases the morbidity and mortality of SLE patients, causing more severe disease and death in SLE.[6-17] The World Health Organization (WHO) has established guidelines for TB prevention in HIV patients.[18] Efforts to prevent TB have been made in HIV patients by administering Isoniazid (INH) prophylaxis and found to significantly reduce the incidence of TB in HIV patients by 35%, with good safety data and no significant increase in drug side effects.[19]

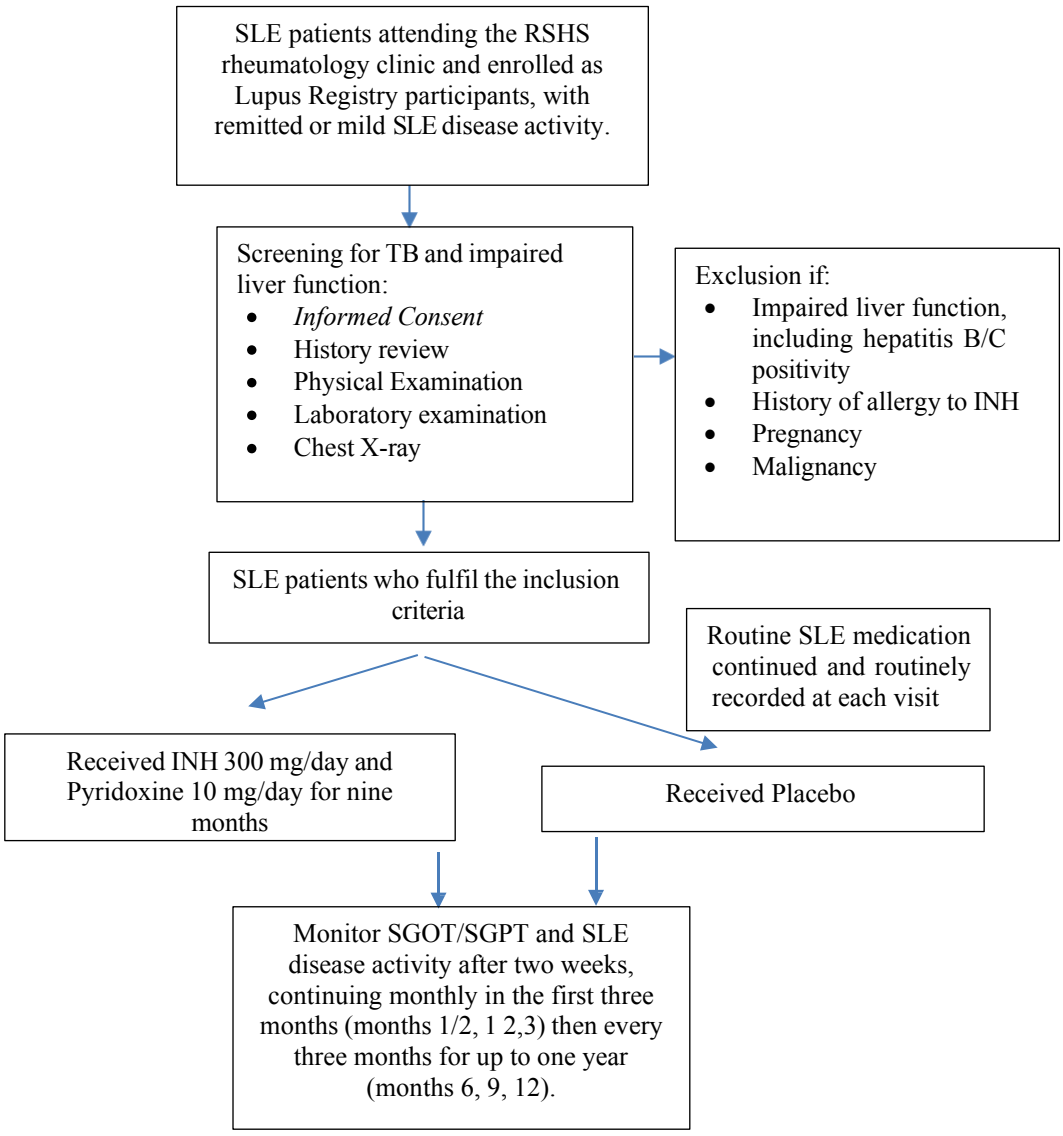
Prevention of TB in SLE is controversial, and no guidelines have been issued on the subject. An Indian study found an 82% reduction in the incidence of TB in SLE patients with INH prophylaxis.[20] However, retrospective studies in Hong Kong and Korea found no significant difference between those given and those not given prophylaxis.[13,21] No studies have specifically examined the safety of INH prophylaxis in SLE patients. Research is needed on the safety of INH in SLE patients, especially in terms of toxicity to the liver and its effect on disease recurrence, before further research on its effectiveness in preventing TB in SLE patients.

Research Design and Subjects

This is a randomized controlled clinical study involving SLE patients at the Rheumatology Polyclinic, Department of Internal Medicine, Padjadjaran University, Hasan Sadikin General Hospital Bandung,

The diagnosis of SLE is based on the 1997 ACR criteria or 2012 SLICC criteria. The screening included *informed consent*, history taking, physical examination, chest X-ray, and laboratory examination (mainly SGOT/SGPT, HBsAg, anti HCV Total). The examination was conducted to ensure that the subjects did not suffer from active TB, and or impaired liver function. Subjects who meet the inclusion criteria will be randomly divided into two groups, the treatment group receiving INH 5 mg/kg/day (maximum 300 mg/day) and pyridoxine 10 mg/day, and the control group receiving neither drug. Routine SLE medications will be continued throughout the study and recorded at each *visit*.

The research design is depicted through the chart below:



Inclusion and Exclusion Criteria

Inclusion Criteria

- SLE patients who do not have signs and symptoms of active TB (pulmonary and extrapulmonary),
- SLE patients who are not on TB treatment,
- SLE patients with no history of TB,
- SLE patients who are in remission or low *disease activity state* (*LLDAS*), with a history of stable SLE treatment in the last three months and have good liver function,
- Agree to fully participate in this study.

Exclusion Criteria

- SLE patients who have previous liver dysfunction, including hepatitis B or hepatitis C,
- SLE patients who have a history of allergy to INH,
- SLE patients with malignancy,
- SLE patients who are pregnant.

Variables

VARIABLES	DEFINITION	ASSESSMENT	OUTPUTS	DATA TYPE
Systemic Lupus Erythematosus (SLE)	ACR 1997 or SLICC 2012 criteria[22,23]	History review, physical examination, laboratory examination	Yes/No	Nominal
Age	Age at the time of study	History review	Year	Numerical
Duration of SLE	Duration from diagnosis of SLE to inclusion in the study.	History review and medical record confirmation	Month	Numerical
Isoniazid (INH) preventive therapy	INH 5 mg/kg/day, max 300 mg/day for nine months	History review	Yes/No	Nominal
Tuberculosis	Active TB.	History review, physical examination, Chest X-Ray, and/or AFB/RMT examination.	Yes/No	Nominal
SLE disease activity [25]	Based on the *SLE disease activity index* (SLEDAI-2K) score: • 0 = remission • 1-5 = mild • 6-11 = moderate • ≥12 = severe	History review, physical examination, laboratory examination	As per score	Nominal
Changes in SLE disease activity[26]	Based on change in *SLE disease activity index* (SLEDAI-2K) score. Change in score: • increased ≥ 3 = relapse • decreased ≥ 3 = improved • increased but < 3 = active persistent	History review, physical examination, laboratory examination	As per score	Nominal
Drug-induced hepatotoxicity (INH)	Increase of more than twice the upper limit of normal SGOT/SGPT values and improvement after drug withdrawal[27]	History review, physical examination, laboratory examination	Yes/No	Nominal

R value[28]	Values used to distinguish the type of damage in drug-induced hepatotoxicity. R = (SGPT value / upper limit of normal SGPT value) / (ALP value / upper limit of ALP value).	Laboratory examination	As per the result value	Numerical
Types of damage in drug-induced hepatotoxicity[28]	Type of damage: • Hepatocellular (SGPT ≥3 upper limit of normal values and *R* ≥ 5). • Cholestatic (ALP ≥2 upper limit of normal value and *R* ≤ 2). • Mixed (SGPT ≥3 upper limit of normal, ALP ≥2 upper limit of normal, and 2 < *R* < 5).	Laboratory examination	According to the type of damage	Nominal
Severity of drug-induced hepatotoxicity[28]	• *Grade* 0 (*No Liver Injury*): the patient can tolerate the drugs and there are no signs and symptoms of hepatotoxicity. • *Grade* 1 (*Mild Liver Injury*): elevated SGPT and/or ALP values, total bilirubin <2.5 upper limit of normal (2.5 mg/dL or 42.75 µmol/L), INR <1.5. Most patients show adaptive processes to liver damage. It may be accompanied or without symptoms, such as fatigue, nausea, anorexia, right upper abdominal pain, jaundice, itching, skin redness, or weight loss. • *Grade* 2 (*Moderate Liver Injury*): elevated SGPT and/or ALP values,	History review, physical examination, laboratory examination	As per *grade*	Ordinal

	with total bilirubin ≥2.5 upper limit of normal or INR ≥1.5. Symptoms and signs of impaired liver function become more apparent. • *Grade* 3 (*Severe Liver Injury*): elevated SGPT and/or ALP, total bilirubin ≥5 upper limit of normal (5 mg/dL or 85.5 µmol/L) with or without INR ≥1.5. Symptoms and signs of hepatic impairment are obvious, indicating the need for hospitalisation. There are no signs and symptoms of hepatic encephalopathy. • *Grade* 4 (*Acute Liver Failure*): evidence of blood clotting disorders with INR ≥1.5 or PTA <40%, signs and symptoms of hepatic encephalopathy, and total bilirubin values ≥10 upper limit of normal (10 mg/dL or 171 µmol/L) or an increase in total bilirubin values ≥1.0 mg/dL (17.1 µmol/L) per day for 26 weeks after the onset of drug-induced hepatotoxicity. Patients may develop ascites and other organ dysfunction. • *Grade* 5 (Lethal): death caused by drug-induced hepatotoxicity.	

Unexpected events[29]	• *Grade* 1 Mild; asymptomatic or mild symptoms only; clinical observation or diagnosis only; intervention not indicated. • *Grade* 2 Moderate; minimal, local or non-invasive interventions are indicated; limitation of daily activities based on age. • *Grade* 3 Severe or medically significant, but not life threatening; indication for hospital admission; limitation of independent daily activities. • *Grade* 4 Life-threatening; indication for rapid/immediate intervention. • *Grade* 5 Lethal; associated with an adverse event.	History review, physical examination, laboratory examination	As per *grade*	Ordinal
Acid Fast Bacilli (AFB)[30]	Staining technique to see acid fast bacilli (*Mycobacterium tuberculosis*) from the sample taken	Laboratory examination	Positive/negative	Nominal
Rapid Molecular Test (RMT)[31]	Rapid PCR (*Polymerase Chain Reaction*) testing using the GeneXpert platform that can detect TB bacteria	Laboratory examination	Positive/negative	Nominal

Research Duration and Time

This research was conducted from August 2022 to December 2024.

Sample size calculation

The sample size calculation was carried out based on INH prophylaxis studies conducted in HIV patients, obtained the risk of *drug reaction* events of RR 1.2, so that with a confidence level of 95%, power 80%, and effect size 0.5, the sample

size of each group was 27 people, plus 10% to 30 people. Thus, the total number of patients involved is 60 people who will be divided into two groups.

Data Analysis

This study was conducted to assess the safety of INH drug administration in SLE patients by analyzing the increase in SGOT/SGPT values and assessing SLE disease activity measured using SLEDAI. Both will be assessed after two weeks of drug or placebo administration, followed by monthly for the first three months (months 1, 2, 3), then every three months until one year (months 6, 9, 12). Statistical tests used were t-test and/or chi-square by comparing two treatment groups. Results were considered significant when the p value was ≤ 0.05. Data processing was performed with SPSS version 26 and Stata version 13.

Outputs

The incidence of TB in SLE patients, especially in endemic countries, is high at 11.4%[32]. This rate is much higher than the normal population. The administration of isoniazid (INH) has been recommended for TB prophylaxis in HIV patients. However, until now there has no guideline or agreement on the administration of INH as TB prophylaxis in SLE patients. Studies of INH as TB prophylaxis in SLE patients have shown mixed results. Safety is one of the aspects considered, given the risk of drug-induced hepatitis. Therefore, a study to evaluate the safety of TB prophylaxis therapy with INH in SLE patients is very important. Furthermore, this study can serve as a base for further research to evaluate the effectiveness of TB prophylaxis therapy with INH in SLE patients.

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Appendix 1

Gantt Chart Timeline Table

Type of Activity	Year 1													Year 2											
	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4
Subject Screening	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■								
Subject Recruitment	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■								
Inspection	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■								
Data Analysis																		■	■	■	■	■			
Report Generation																					■	■	■	■	
Publication of Results																									■

Appendix 2

CRF INH Safety Study in SLE Patients:
Initial Screening

Subject Number_____
MR Number: □Inpatient _____□ Rheumatology Clinic _____
Full Name: _____Gender: □F/ M □
Date of Birth (*day/month/year*): ____/____/____ Tel/Phone: _____
Full Address: _____
Occupation: _____Education: _____Ethnic: _____
Marital Status: _____Date of SLE diagnosis (*month/year*): ____/____

Visit 0 Date (*day/month/year*): ___/___/___

Clinical (TB, SLE, Liver Disease, Pregnancy)	Routine Lab data screening			Chest X-Ray
History review History: • Tuberculosis (TB): □Ever□ Never□ Don't Know • *Liver/Liver* Disease: □Ever□ Never□ Don't Know • Allergy to INH: □ Yes□ No□ Don't Know • Malignancy/Cancer: □ Yes□ No□ Don't Know • Currently on TB treatment: □ Yes□ No□ Don't Know • Currently pregnant□ Yes□ No□ Don't Know	Hb			
	Ht			
	Leukocytes			
	Platelets			
	Count Type	Basophils		
		Eosinophils		
		Neutrophil Rod		
		Neutrophil Segment		
		Monocytes		
		Lymphocytes		
	ESR			
	SGOT			
	SGPT			
	HBsAg			
	Anti HCV			
	Creatinine			
Physical Examination	Urinalysis	Proteinuria		
		Erythrocytes		
		Leukocytes		
		Cylinders		

*When Clinically Suspicious of TB

Date	Chest X-Ray	AFB	RMT

Active TB: □ Yes (Clinical/Bacteriological) □ No

SLEDAI

Parameters	Score	Total	Parameters	Score	Total
Seizures	8		Arthritis	4	
Psychosis	8		Myositis	4	
Organic Brain Syndrome	8		Cylinders	4	
Visual Impairment	8		Haematuria	4	
Cranial Nerve Abnormalities	8		Proteinuria	4	
Lupus Headache	8		Piuria	4	
Cerebrovascular	8		Pleuritis	2	
Vasculitis	8		Pericarditis	2	
New Malar Rash	2		Low complement	2	
Alopecia	2		Anti-dsDNA increased	2	
New/recurrent ulcers	2		Thrombocytopenia	1	
Fever	1		Leukopenia	1	

SLEDAI Total Score: ____□ 0 (Remission)□ 1-5 (Mild)□ 6-11 (Moderate) □≥ 12 (Severe)

SLE medications: Take SLE medications regularly: □ Yes □ No

Medicine	Dosage	Start date	Stop date
□ Prednisone/equivalent	mg/day		
□ *Pulse Steroids*	mg/day		
□ HCQ/CQ	mg/day		
□ Methotrexate	mg/week		
□ Azathioprine	mg/day		

□ MMF	mg/day		
□ Mycophenolic acid	mg/day		
□ Leflunomide	mg/day		
□ Cyclosporin	mg/N		
□ Tacrolimus	mg/day		
□ Cyclophosphamide	□NIH□ EuroLupus		
□ Rituximab			
□ More			

CRF INH Safety Study in SLE Patients: Follow Up

Subject Number_____No Drug Study_____
MR Number: □Inpatient _____□ Rheumatology Clinic _____
Full Name: _____Gender: □F/ M □
Date of Birth (*day/month/year*): ____/____/____ Tel/Phone: _____

Visit (___months from visit __) Date (*day/month/year*): __/__/___
Take medication regularly: □ Yes□ No

Clinical	Laboratory		
History review □ Fever □ Malaise □ Fatigue □ Abdominal Pain □ Nausea □ Vomiting□ Icteric □ Others:	Hb		
	Ht		
	Leukocytes		
	Platelets		
	Count Type	Basophils	
		Eosinophils	
		Neut Rod	
		Neut Segment	
		Monocytes	
		Lymphocytes	
	ESR		
Physical Examination	SGOT		
	SGPT		
	Creatinine		
	Urinalysis	Proteinuria	
		Erythrocytes	
		Leukocytes	
		Cylinders	

SLEDAI Score:
SLEDAI Total Score: ___□ 0 (Remission)□ 1-5 (Mild)□ 6-11 (Moderate) □≥ 12 (Severe)
SLE Disease Activity: □ Relapse□ Improving□ Persistently Active□ Remission

Elevated SGOT/SGPT≥ 2x Upper limit of normal values: □ Yes□ No

Liver function disorders: □ Hepatocellular□ Cholestatic□ Mixed
Severity: □ 0 (*No Liver Injury*)
□ 1 (*Mild Liver Injury*)
□ 2 (*Moderate Liver* Injury)
□ 3 (*Severe Liver Injury*)
□ 4 (*Acute Liver Failure*)
□ 5 (*Lethal*)

Management of Drug-Induced Hepatoxicity

□ INH discontinue □ Continue INH Administration
□ Other medications: _____ _____
_____
_____
_____

Drug-induced hepatotoxicity outcomes

_____
_____
_____
_____

CRF INH Safety Study in SLE Patients:
SLE recurrence

Subject Number_____
Full Name: _____Gender: □F/ L □
Date of Birth (*day/month/year*): _____/_____/_____ Tel/Phone: _____

Visit (___months from visit ___) Date (*day/month/year*): ___/___/___

SLEDAI score (at time of screening): _____□ Remission □ Mild □ Moderate □Severe

Previous SLEDAI scores: _____

Diagnosis of SLE Recurrence

Clinical (SLE)
History review
Physical Examination

Management of SLE Recurrence (based on rheumatologist's judgement)
□ INH discontinue
□ Continue INH
□ Changes in SLE medications (see CRF for SLE medications, any changes should be noted on the CRF)
□ Other medications:_____ _____
_____
_____
_____

SLE Recurrence Outcome

Outputs	**SLEDAI Score**	**Date (*day/month/year*)**
□ Relapse		
□ Improving		
□ Active Persistent		
□ Remission		
□ Died		
□ Others:		

CRF INH Safety Study in SLE Patients:
SLE medications

No Subject _____
Full Name: _____Gender: □F/ M □
Date of Birth (*day/month/year*): ____/____/____ Tel/Phone: _____

Visit (___months from visit ___) Date (*day/month/year*): ___/___/___

Take SLE medication regularly: □ Yes □ No

SLE medications

Medicine	Dosage
□ Prednisone or equivalent	mg/day
□ *Pulse Steroids*	mg/day
□ HCQ/CQ	mg/day
□ Methotrexate	mg/week
□ Azathioprine	mg/day
□ MMF	mg/day
□ Mycophenolic acid	mg/day
□ Leflunomide	mg/day
□ Cyclosporin	mg/N
□ Tacrolimus	mg/day
□ Cyclophosphamide	□NIH□ Euro Lupus
□ Rituximab	
□ Belimumab	
□ Others:	

INFORMED CONSENT

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PADJADJARAN UNIVERSITY

INFORMATION

" Study on the Safety of Administering Isoniazid to Systemic Lupus Erythematosus Patients to Prevent Tuberculosis "

I am Dr. Laniyati Hamijoyo, dr., SpPD-KR, I am a rheumatologist at the Faculty of Medicine, Padjadjaran University / Hasan Sadikin Hospital Bandung. My team and I are conducting a study to determine safety of Isoniazid (INH) to prevent Tuberculosis (TB) in Systemic Lupus Erythematosus (SLE) patients. SLE patients are susceptible to TB disease. This is due to their autoimmune condition, as well as the corticosteroid and/or immunosuppressant drugs taken by the patient. Indonesia has the second highest number of TB cases in the world and remains a TB endemic country to date. TB suffered by people with SLE can cause severe problems, especially in terms of disease recurrence (lupus becomes active) which can worsen the patient's condition. Therefore, TB should be prevented. One form of prevention that can be done is the administration of Isoniazid (INH) therapy for nine months. Through this, SLE patients are expected to avoid TB. We invite you to participate in this study. Your participation in this study is voluntary, so you can decide whether or not to participate.

Research Objectives:

The aim of this study was to determine the safety of Isoniazid (INH) therapy to prevent TB in SLE patients.

Why the subject was chosen:

You were selected as a respondent because you met the criteria intended by the researchers, namely SLE patients with a low degree of disease activity/remission, not currently undergoing TB therapy, no history of TB, no symptoms/signs of active TB disease, no liver function disorders, no history of allergy to INH drugs, and willing to participate in this study until completion.

Procedure:

This study will be conducted by taking blood samples and performing Chest X-Ray for initial screening. If you meet the criteria, you will be divided into two groups. One group will receive INH therapy at a dose of 5 mg/kg BW/day (maximum 300 mg) and vitamin B6 10 mg/day, while the other group will receive placebo (no INH/Vitamin B6). The drugs will be consumed for nine months. The side effects of the drugs and lupus disease activity will be monitored through monthly blood tests in the first three months (months 1/2, 1, 2, 3) and every three months until month 12 (months 6, 9, 12). If necessary, a chest X-Ray and/or sputum examination will be done to confirm whether you have TB or not.

Risk and inconvenience:
Possible risks include discomfort during blood collection, hematoma (blue-black bruising) at the site of blood collection and exposure to X-Ray radiation. Other possible risks include nausea, jaundice, bloating, and impaired liver function.

Benefits (direct to subject and general):
Public benefit: This study may serve as a guide for physicians treating SLE patients to provide TB preventive therapy, especially for those living in TB-endemic areas.
Direct benefits obtained by the subject: knowing the status of disease activity, getting screened for TB, and obtaining TB prevention therapy.

Alternative procedure:
None.

Data confidentiality:
We will guarantee the confidentiality of information relating to your identity and will not be known by unauthorized persons. The results of this study will be published without mentioning your identity.

Estimated number of subjects to be included:
The subjects to be included in this study were 60 SLE patients.

Volunteerism:
Your participation in this study is voluntary.

Subject Participation Period:
This research is planned to take place August 2022 to December 2024. If you have followed the study completely, your participation in this study is considered complete.

Subjects may be excluded/resigned from the study:
If during the implementation of the study you want to withdraw or do not want to continue, then you are allowed to withdraw before the data collection process is carried out.

Possible financing from health insurance companies or researchers:
No insurance will be provided to you in this study. If side effects occur due to the INH medication, you will be closely monitored and treated for any possible side effects, such as nausea, vomiting or itching. If hospitalization is required, all treatment costs will be the responsibility of the researcher.

Incentives and compensation:
If you are willing to participate in this study, you will be compensated in the form of transport money totaling IDR 50,000 per visit (six visits) until the completion of the study.

Question:
If there are any questions regarding this study, respondents can contact the researcher at the rheumatology clinic of Dr. Hasan Sadikin Hospital.

Researcher:
Dr. Laniyati Hamijo, dr., SpPD-KR
Mobile Number: +6281223032863

Research Assistant:
dr. Naurah Alzena Hana Dhea
Mobile Number: +6281312126312

APPROVAL AFTER EXPLANATION TO
PARTICIPATE IN THE RESEARCH
(*INFORMED CONSENT*)

I have read or obtained an explanation, fully realize, understand, and understand the purpose, benefits, and risks that may arise in the research, and have been given the opportunity to ask questions and have been answered satisfactorily, as well as at any time can withdraw from participation, then I **agree / do not agree**[*)] participate in this study, entitled:

"**Study on the Safety of Administering Isoniazid to Systemic Lupus Erythematosus Patients to Prevent Tuberculosis**"

I voluntarily choose to participate in this study without any pressure. I will be given a copy of the explanation sheet and signed consent form for my records.
I agree:
Yes/No [*)]

	Date	Signature (if not possible, thumbprint can be used)
Participant Name: Age: Address:		
Researcher Name:		
Witness Name:		

*) cross out unnecessary

Appendix 4. Ethical Approval

KEMENTERIAN PENDIDIKAN, KEBUDAYAAN,
RISET DAN TEKNOLOGI
UNIVERSITAS PADJADJARAN
KOMISI ETIK PENELITIAN
RESEARCH ETHICS COMMITTEE
Jl. Prof. Eyckman No. 38 Bandung 40161
Telp. & Fax. 022-2038697 email: kep@unpad.ac.id, website: kep.unpad.ac.id

No. Reg.: 2110071088

PERSETUJUAN ETIK
ETHICAL APPROVAL

Nomor: 305/UN6.KEP/EC/2022

Komisi Etik Penelitian Universitas Padjadjaran Bandung, dalam upaya melindungi hak asasi dan kesejahteraan subjek penelitian serta menjamin bahwa penelitian berjalan sesuai dengan pedoman *International Conference on Harmonisation – Good Clinical Practice (ICH-GCP)* dan aturan lainnya yang berlaku, telah mengkaji dengan teliti dan menyetujui proposal penelitian berjudul:

The Research Ethics Committee Universitas Padjadjaran Bandung, in an effort to protect the basic rights and welfare of the subject of the research and to assure that a research operates in accordance with International Conference on Harmonisation – Good Clinical Practice (ICH-GCP) guidlines and other applicable laws and regulations, has throughly reviewed and approved a reaserch proposal entitled:

"STUDI KEAMANAN PEMBERIAN OBAT *ISONIAZID* PADA PASIEN LUPUS ERITEMATOSUS SISTEMIK UNTUK MENCEGAH TERJADINYA INFEKSI TUBERKULOSIS"

Nama Peneliti Utama *Principal Researcher*	:	Dr. Laniyati Hamijoyo, dr. SpPD-KRM.Kes
Pembimbing/Peneliti Lain *Supervisor/Other Researcher*	:	Edhyana K. Sahiratmadja, dr., Ph.D Bachti Alisjahbana, dr., SpPD-KPTI., PhD Guntur Dharmawan, dr SpPD
Nama Institusi *Institution*	:	Departemen Imunologi Fakultas Kedokteran Universitas Padjadjaran

proposal tersebut dapat disetujui pelaksanaannya.
hereby declare that the proposal is approved.

Ditetapkan di : Bandung
Issued in
Tanggal : 31-03-2022
Date

Ketua,
Chairman,

Nur Atik, dr, M.Kes., PhD
NIP. 19811010 200801 1 019

Keterangan/notes:
Persetujuan etik ini berlaku selama satu tahun sejak tanggal ditetapkan.
This ethical clearance is effective for one year from the due date.
Pada akhir penelitian, laporan pelaksanaan penelitian harus diserahkan ke Komisi Etik Penelitian.
In the end of the research, progress and final summary report should be submitted to the Research Ethics Committee.
Jika ada perubahan atau penyimpangan protokol dan/atau perpanjangan penelitian, harus mengajukan kembali permohonan kajian etik penelitian.
If there be any protocol modification or deviation and/or extension of the study, the Principal Investigator is required to resubmit the protocol for approval.
Jika ada kejadian serius yang tidak diinginkan (KTD) harus segera dilaporkan ke Komisi Etik Penelitian.
If there are Serious Adverse Events (SAE) should be immediately reported to the Research Ethics Committee