THESIS PROTOCOL

TITLE

Effect of Difelikefalin on CKD-Associated Pruritus in Patients on Maintenance Hemodialysis: A Randomized, Placebo-Controlled Trial

NCT Number: Not Yet

Date:April 2026

INVESTIGATOR:

Dr. Md.Shariful Islam Sarker

Resident Student

MD (Nephrology) Phase-B

Session: March, 2024

GUIDE:

Prof. Dr. Md Nurul Huda

MBBS, MCPS (Medicine), FCPS (Medicine),

MD (Nephrology), FISN,FASN

Professor and Head

Department of Nephrology

Chittagong Medical College and Hospital

CO-GUIDE:

Dr. Mohammad Shafiul Haider Chowdhury

MBBS, MD (Nephrology)

Associate professor

Department of Nephrology

Chittagong Medical College and Hospital

To

The Principal
Chittagong Medical College
Chattogram.

Subject: Application for the approval of Thesis Protocol with the title**"Effect of Difelikefalin on CKD-Associated Pruritus in Patients on Maintenance Hemodialysis: A Randomized, Placebo-Controlled Trial"**

Sir,

With due respect and humble submission, I would like to state that I am a student of MD Phase B (Nephrology), at BSMMU, Dhaka. As per requirement of the course, I would like to perform my research work on the thesis with the above-mentioned title under the direct supervision of Prof. Dr. Md Nurul Huda, Professor and Head, Department of Nephrology, Chittagong Medical College and Hospital, Chattogram, Bangladesh.

I therefore, like to request you to approve my protocol so that I can commence my work in your esteemed institute to complete my thesis in due time.

Obediently Yours

Dr. Md.Shariful Islam Sarker
MD (Nephrology-Phase B)
Department of Nephrology
Chittagong Medical College and Hospital
Chattogram, Bangladesh

CMC Ethical Review Committee

Chattogram Medical College
Chattogram-4000, Bangladesh
Tel-031619400, Fax-630180

Application for Ethical Clearance of Studies for post-Graduate Thesis

1.	Name of the applicant	:	**Dr. Md.Shariful Islam Sarker**
2.	Course	:	MD (Nephrology –Phase B)
3.	Category	:	Government
4.	Title of the study	:	**"Effect of Difelikefalin on CKD-Associated Pruritus in Patients on Maintenance Hemodialysis: A Randomized, Placebo-Controlled Trial"**
5.	Type of the study	:	Randomized, placebo-controlled, double-blinded, single-center trial
6.	Duration of the study	:	One Year & Six months
7.	Any collaboration	:	No
8.	Conflict of interest	:	None
9.	Name of the Guide	:	Prof. Dr. Md Nurul Huda, Professor and Head, Department of Nephrology Chittagong Medical College and Hospital Chattogram, Bangladesh
10.	Name of the Co-Guide	:	Dr. Mohammad Shafiul Haider Chowdhury MBBS, MD (Nephrology) Associate professor Department of Nephrology Chittagong Medical College and Hospital.

Check Documents being submitted herewith to committee:

1.	Summary	**:** Attached
2.	Umbrella proposal initially	**:** NA
3.	Protocol and CRF	**:** Attached
4.	Informed consent form for subject	**:** Attached
5.	Verbal consent form for subjects	**:** NA
6.	Procedure for Maintaining Confidentiality	**:** Attached
7.	Schedule of the study	**:** Attached

Declaration

I agree to obtain approval of the Ethical Review Committee for any changes involving the rights and welfare of subjects or any changes of the methodology before making any such changes.

……
Principal investigator/Student

Dr. Md.Shariful Islam Sarker
MD (Nephrology-Phase B)
Department of Nephrology
Chittagong Medical College and Hospital
Chattogram, Bangladesh

Forwarding from the Guide

……
Guide

Prof. Dr. Md Nurul Huda,
Professor and Head,
Department of Nephrology,
Chittagong Medical College and Hospital,
Chattogram, Bangladesh

CHITTAGONGMEDICAL COLLEGE

Application for the Ethical review of thesis protocol

1.	Name of the applicant	:	Dr. Md.Shariful Islam Sarker
2.	Course	:	MD (Nephrology Phase B)
3.	Category	:	Government
4.	Title of the study	:	**"Effect of Difelikefalin on CKD-Associated Pruritus in Patients on Maintenance Hemodialysis: A Randomized, Placebo-Controlled Trial"**
5.	Type of the study	:	Randomized, placebo-controlled, double-blinded trial
6.	Duration of the study	:	One Year & Six months
7.	Any collaboration	:	No
8.	Conflict of interest	:	None
9.	Name of the Guide	:	Prof. Dr. Md Nurul Huda, Professor and Head, Department of Nephrology Chittagong Medical College and Hospital, Chattogram, Bangladesh
10.	Name of the Co-Guide	:	Dr. Mohammad Shafiul Haider Chowdhury MBBS, MD (Nephrology) Associate professor Department of Nephrology Chittagong Medical College and Hospital Chattogram, Bangladesh.
11.	Signature of the Guide	:	
12.	Signature of the Co-Guide	:	
13.	Submission date	:	
14.	Signature of the Student	:	

For Official use:
Serial No: Received on: Reviewed on:
Comment:

Member-Secretary ERB Chairperson ERB

Circle the appropriate answer to each of the following

1. Source Population:			**4. Are subjects clearly informed about:**		
(a) Ill Subjects	√Yes	No	(a) Nature and purpose of the study	√Yes	No
(b) Non* ill subjects	Yes	√No	(b) Procedures to be followed including alternatives used	√Yes	No
(c) Minors or persons under guardianship	Yes	√No	(c) Physical risks	√Yes	No
			(d) Private questions	√Yes	No
2. Does the study involve:			(e) Invasion of the Body	√Yes	No
(a) Physical risks to subjects	√Yes	No	(f) Benefits to be Derived	√Yes	No
(b) Social risks	Yes	√No	(g) Right to refuse to participate or withdraw from the study	√Yes	No
(c) Psychological risks to subjects	Yes	√No	(h) Confidential handling of data	√Yes	No
(d) Discomfort to Subjects	√Yes	No	(i) Compensation where there are risks or loss of working time or privacy is involved in any particular procedure	√Yes	No
(e) Invasion of the body	√Yes	No			
(f) Invasion of privacy	Yes	√No			
(g) Disclosure of information damaging to subject or others	Yes	√No	**5. Will informed consent be required**		
			(a) From subject	√Yes	No
			(b) From parent or Guardians	Yes	√No
3. Does the study involve:					
(a) Use of records (hospital, medical, death, birth or other)	Yes	√No	**6. Will precautions will be taken to protect anonymity of subjects**	√Yes	No
(b) Use of fetal tissue or abortus	Yes	√No			
(c) Use of organs or body fluids	Yes	√No			

(If not Applicable write NA)

Chittagong Medical College
Chattogram-4000, Bangladesh
Tel-031619400, Fax-630180

Research Proposal

For Post Graduate Thesis/Dissertation

Part - A

1.	Title of the study	:	**"Effect of Difelikefalin on CKD-Associated Pruritus in Patients on Maintenance Hemodialysis: A Randomized, Placebo-Controlled Trial"**
2.	Name of the applicant	:	Dr. Md.Shariful Islam Sarker
3.	Course	:	MD (Nephrology Phase B)
4.	Place of Study	:	Department of Nephrology, Chittagong Medical College Hospital, Chattogram.
5.	Sponsoring	:	Not Applicable
6.	Duration of the study	:	One and half years.
7.	Date of Commencement	:	
8.	Date of completion		
9.	Total cost	:	3,75,120/=
10.	Other support of proposed research		
	i. : In this research project being supported by any other source?		No
	ii. Has an application for funding of this project has been submitted to any other organization (s)?		No
11.	Date of submission	:	
12.	Signature of student	:	
13.	Signature of Guide	:	
14.	Endorsement of the course coordinator		

Name and Signature

Designation

Official Seal

Part – B

Student's Information Sheet

1. Name : Dr. Md.Shariful Islam Sarker
   Designation : Student, MD (Nephrology Phase B)
   Official address with telephone & mail : Department of Nephrology, Chittagong Medical College Hospital, Chattogram
   Phone:01738647201
   Email:sobujshariful@gmail.com
   Present residential address :
2. Academic Background :

Degree	**Institute**	**University/Board**	**Field**	**Year**
M.B.B.S			Passed	

3. Field of study : Nephrology
4. Research experience : None
5. Percentage of time to be devoted to this project : 100%
6. Number of Scientific Publication : None

……..

Signature of the Student

PART-C

Summary

Background: Pruritus is a common and distressing symptom among hemodialysis patients with chronic kidney disease (CKD), significantly impacting their quality of life. Difelikefalin, a selective kappa-opioid receptor agonist, has shown promise in alleviating CKD associatedpruritus(CKDaP) However, its efficacy and safety in the Bangladeshi population remain under-explored. **Objectives:**This study aims to evaluate the effect of Difelikefalin, compared to placebo, in reducing pruritus, improving quality of life in CKD patients on maintenance hemodialysis.**Materials and Methods:** A randomized, placebo-controlled trail, double-blinded, will be conducted in the Department of Nephrology of chittagong Medical College Hospital ,Chattogram ,Bangladesh for one and half years. A total of one hundred two CKD patients on maintenance hemodialysis will be included in this study.Patient with moderate-to-severe pruritus (Worst Itching Intensity Numerical Rating Scale [WI-NRS] score ≥ 4) will be enrolled and randomly assigned in a 1:1 ratio to receive either Difelikefalin (0.5 mcg/kg) or a placebo intravenously after each heamodialysis for 6 weeks. The primary outcome measure will be the change in WI-NRS score from baseline to week 6. Secondary outcomes will be measured by Skindex 10 scale.Adverse events and safety measures will also be recorded. The primary analysis will follow either an intention-to-treat or a per-protocol approach and will be performed using SPSS version 27.**Discussion:**Data from previous studies indicate that Difelikefalin can reduce the severity of itching and improve the quality of life in CKD patients on maintenance hemodialysis. Clinical trials are needed to better understand the safety and efficacy of Difelikefalin in CKD patients in our population.

PART-D

1. Introduction:

Chronic kidney disease-associated pruritus (CKD-aP), alternatively termed Uremic pruritus (UP), represents a frequent, distressing, and often incapacitating clinical manifestation among individuals diagnosed with chronic kidney disease (CKD) or end-stage renal disease (ESRD) (Elhag et al., 2022; Elsayed et al., 2023). Characterized by persistent, intense itching—typically generalized but occasionally localized—CKD-aP disproportionately affects patients undergoing hemodialysis, with epidemiological studies reporting a strikingly variable prevalence ranging from 22% to 84% in this population. Notably, a substantial subset of these patients, approximately 20–40%, endure moderate-to-severe pruritus, which profoundly diminishes their quality of life (Daraghmeh et al., 2022; Rehman et al., 2018).

The ramifications of CKD-aP extend far beyond superficial discomfort. The condition is intricately linked to a constellation of physical and psychological burdens, including chronic sleep disturbances such as insomnia, relentless fatigue, and dermatological complications arising from repetitive scratching, such as excoriations, lichenification, and secondary infections (Lu et al., 2021; Lu et al., 2022). Psychosocially, patients frequently grapple with emotional distress, including feelings of embarrassment, social withdrawal, and stigmatization due to visible skin lesions, which may exacerbate preexisting mental health challenges like anxiety, depression, and irritability. Furthermore, emerging evidence underscores a concerning association between CKD-aP and elevated mortality risks; dialysis-dependent patients with CKD-aP exhibit higher rates of all-cause mortality, as well as increased fatalities linked to cardiovascular events and systemic infections, suggesting a potential interplay between chronic inflammation, immune dysregulation, and disease progression (Grochulska et al., 2019; Sukul et al., 2021).There is, therefore, a need for effective interventions for the treatment of CKD-aP.Off-label treatments may include antihistamines, topical corticosteroids, and gabapentin or pregabalin; although there are reports that treatments like gabapentin and pregabalin are effective at reducing itch, their side effects sometimes prevent their use in this patient population (Hercz et al., 020; Skrzypczak et al., 2024).

The pathogenesis of CKD-aP is incompletely understood.Several hypotheses have been proposed, including metabolic disturbances, dysregulated immune response, and imbalances in the endogenous opioid system, with peripherally distributed kappa opioid receptors potentially playing a role (Brennan 2024; Skrzypczak et al., 2024).

Difelikefalin is a peripherally restricted, selective kappa opioid receptor agonist that exerts antipruritic effects by means of activation of kappa opioid receptors on peripheral neurons and immune cells (Gardell, et al., 2008). The hydrophilic small-peptide structure restricts passive diffusion across membranes, thereby limiting access to kappa opioid receptors in the central nervous system (O'Connor et al., 2010).

European Medicines Agency (EMA) and Federal Drug Administration (FDA) approved difelikefalin, the first drug specifically indicated for CKD-aP in dialyzed patients, which demonstrated efficacy in two Phase 3 clinical trials (Topf et al., 2022). The development of this targeted medication, supported by solid evidence of its effectiveness and safety, increased awareness and understanding of this condition (Buades et al., 2024). According to the most current expert recommendations, difelikefalin should be first-line medication for patients with moderate-to-severe CKD-aP undergoing dialysis (Agarwal et al., 2022; Skrzypczak et al., 2024).13 Other therapies should only be considered as first-line choice for those patients only if difelikefalin is not available (Agarwal et al., 2022; Skrzypczak et al., 2024).

Although difelikefalin showed promise as a treatment for CKD-aP in dialyzed patients, particularly through its selective κ-opioid receptor agonist activity, the current body of evidence has limitations. Approximately 20% of patients did not report clinically meaningful reductions in itch intensity, 30% did not present clinically relevant improvements in QoL (Weiner et al., 2022). Several studies, including the pivotal KALM-1 and KALM-2 trials, demonstrated significant efficacy in reducing itch intensity and improving quality of life in hemodialysis patients (Topf et al., 2022).

Defelikefalin's safety varies according to dose. Regarding safety, the majority of research revealed that adverse effects increased in frequency in a way that was dose dependent. Across all trials, nausea, vomiting, dizziness, diarrhea, and disturbances in gait were the most frequently reported adverse events (Enggalhardjo, et al., 2024). A dosage of 0.5 μg/kg of difelikefalin proved to have the most favorable benefit-risk profile, and it was safe to use up to 1.0 μg/kg (Narita et al., 2022).

Though difelikefalin appears to be a promising agent for the management of CKD-aP, evidence is still under-powered due to the paucity of the current data; therefore, more robustrandomized controlled trials (RCTs)are required to confirm the benefit of difelikefalin (Saeed et al., 2024).

While recent clinical trials in Western populations have demonstrated its efficacy, data from low- and middle-income countries, such as Bangladesh, are scarce. The prevalence of CKD in Bangladesh surpasses the global and even South Asian averages.About 20 million people are suffering from chronic kidney disease, and of them, approximately 35,000–40,000 develop ESRD each year (MostafiandJabin 2023). This trial aims to evaluate the superiority of Difelikefalin over placebo in reducing pruritus severity among hemodialysis patients in a tertiary-level teaching hospital in Bangladesh.

2. Rationale

Pruritus in hemodialysis patients is a chronic and highly irritating condition associated with chronic kidney disease (CKD) that adversely affects sleep, mood, social participation and overall quality of life. The commonly used agents for CKD-associated pruritus often have limited efficacy or tolerability in many patients. Oral medications used to manage this condition are frequently associated with poor compliance due to a high pill burden. On the other hand, intravenous administration of difelikefalin after hemodialysis offers a practical and patient-friendly alternative. It uses the same dialysis access, avoiding the need for extra needle insertions. Previous studies have demonstrated that difelikefalin improves outcomes in patients with CKD-associated pruritus and enhances their quality of life. To my extensive search, data regarding the use of difelikefalin for CKD-associated pruritus in our population is scarce. This study aims to explore the effect of difelikefalin on CKD-associated pruritus in maintenance hemodialysis (MHD) patients in our population.

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3.1. Research questions:

- What is the effect of difelikefalin on CKD-associated pruritus in patients on maintenance hemodialysis?

3.2 Research hypothesis:

- Difelikefalin effectively reduces CKD–associated pruritus in maintenance hemodialysis patients.

4. Objectives

4.1 General objective:

- To evaluate the effect of difelikefalin in CKD-associated prurituson maintenance hemodialysis patients.

4.2 Specific objectives:

I. To determine the baseline scores of the WINRS scale and Skindex-10 scale in CKD-associated pruritus on maintenance hemodialysis patients..

II. To estimate and compare the changes in the WINRS scale, and Skindex-10 Scale between the experimental and control groups.

III. To assess the tolerability and detect any adverse effect of Difelikefalin in patients with CKD-associated pruritus on maintenance hemodialysis throughout the study period.

5. Materials and method:

5.1. Type of study: Randomized, placebo-controlled,double-blinded trial,

5.2 Place of Study: Department of Nephrology, Chittagong Medical College Hospital, Chattogram, Bangladesh.

5.3 Study period: One and half years from acceptance of protocol.

5.4 Study population: Adult CKD stage-5 patients on MHD in the dialysis unit ofthe Department of Nephrology,CMCH during the study period.

5.5 Study groups: Based on the interventions,there will be two groups in the study

I. Experimental group:

Standard symptomatic treatment for itching + Intravenous difelikefalin

II. Control group:

Standard symptomatic treatment for itching + Placebo

5.6 Sampling technique: Consecutive sampling. From the Selected participants, the intervention and control will be randomly assigned in a 1:1 ratio (block size of four) through computer- generated randomization.

5.7. Inclusion criteria:

i. Adults aged ≥18 years.

ii. Patient with chronic kidney disease on HD for ≥ 3 months.

iii. Moderate-to-severe pruritus (WI-NRS score ≥4).

iv. Able to communicate clearly with the Investigator .

v. Willing and able to provide written informed consent prior to participating in this study.

5.8 Exclusion criteria

i. Known case of Primary skin disesease associated with Itching.

ii. Known case of liver disease.

iii. Known case of iron defeciency anaemia ,hematological malignancy.

iv. Known case of hypothyroidism & hyperthyroidism.

v. Known case of allergic reaction to Opiates .

vi. Pregnancy.

vii. Drug abuse, or substance dependence.

5.9. Sample size: Sample size calculation for hypothesis testing of difference between two proportions:

$$n = \frac{p(100-p) + q(100-q)}{(p-q)^2}\left(z_\alpha + z_\beta\right)^2$$

Where,

Z_α = Z value of standard normal distribution at a definite level of significance
Z_β = Z value of standard normal distribution at a definite level of power
p = Proportion of patients with expected outcome (response rate) in the experimental group
q= Proportion of patients with expected outcome (response rate) in the control group

Here,

Z_α= 1.96 at 95% Confidence Interval
Z_β =1.63 at 95 % power
p= 64% (Fishbane et al., 2020b)
q= 29% (Fishbane et al., 2020b)

So,

$$n = \frac{64(100.0-64) + 29(100.0-29)}{(64-29)^2}(1.96+1.63)^2 \approx 46$$

Considering 10% lost to follow-up final sample will be

$$(46 + 46 \times 10\%) \approx 50.6 \approx 51$$

That means 51 patients in each group will be needed in each group to test the hypothesis.

5.10. List of variables

Variables	Type	Value	Expression
Clinical			
Age	Discrete	In completed years	Mean±SD
Sex	Categorical	Male/Female	Frequency (%)
Duration of HD	Discrete	In completed years	Mean±SD
Duration of prutitus	Discrete	In completed months	Mean±SD
Cause of CKD	Categorical	GN/HTN/DM	Frequency (%)
Baseline use of antipruritic medication	Categorical	Absent/Present	Frequency (%)
WI-NRS score	Discrete	0-10	Mean±SD
Skindex-10 scale total score	Discrete	0-60	Mean±SD
Biochemical			
Calcium	Continous	mmol/l	Mean±SD
Phosphate	Continous	mmol/l	Mean±SD
PTH	Continous	pg/ml	Mean±SD

Operational definitions:

- **Chronic Kidney Disease-Associated Pruritus**: CKD-aPis defined as severe and persistent itching directly related to kidney disease, without other underlying skin or systemic causes to explain the itching. (Hector alve..et al 2020)

- **MHD**: Maintenance haemodialysis was defined as regular haemodialysis treatment for at least 3 months for the management of ESKD.(Mambap, A.T., Che, I.A., Mahamat, M. *et al.* 2022)

- **Skindex-10**: The Skindex-10 scale was developed specifically for uremic pruritus and measures the weekly effect of itch across three domains (disease, mood and emotional distress, and social functioning) Scores on the Skindex-10 scale range from 0 to 60, with higher scores indicating worse itch-related quality of life. (Mathur et al., 2010).

- **Moderate-to-severe pruritus** will be defined as a mean score of >4 points on the 24-hour WI-NRS score calculated.Itching severity scores have been categorized in the literature as mild (<4), moderate (≥4 to<7), or severe (≥7) (Reich et al., 2012).

- **Efficacy outcomes**: The primary efficacy outcome will be the percentage of patients who will have an improvement (decrease) of at least 3 points from baseline at week 6 in the weekly mean score on the daily WI-NRS (Fishbane et al., 2020). The prespecified secondary efficacy outcomes will be the mean change from baseline at week 6 in the Skindex-10 scale total score (Fishbane et al., 2020).

- **Standard Symptomatic Treatment for Itching**: Standard Symptomatic treatment using antihistamin is useful. Gabapentin or Pregabalin UVB therapy ,oral charcoal or nalfuralfine might be the next line of therapy.(Mettang and kremer 2014)

5.11. Data collection instrument: A structured pretested case record form.

5.12. Data collection procedure:

Baseline assessment: CKD patients in HD will be screened consecutively and prospectively by the above inclusion and exclusion criteria to select eligible patients. Eligible patients and their legal relatives will then fully explain the study protocol, their role in the study, and the risks of the study. They will be informed of their right to withdraw from the study at any stage. After getting written informed consent, they will be finally enrolled in the study. Detailed history clinical examination and relevant investigation will be done. Baseline demographic, clinical and biochemical information will be collected from the patients using the case record form and the scales. Blood samples will be collected after an overnight fasting period, with all aseptic precaution 5 mL of venous blood drawn into appropriate vacutainers. iPTH will be measured using a chemiluminescence immunoassay (CLIA).Serum calcium and phosphate will be analyzed using colorimetric methods on a Beckman Coulter AU480 or equivalent validated clinical chemistry analyzer.

Allocation: Once a participant is enrolled in the study and consents to participate, they will be assigned to a treatment group according to the randomization sequence. This assignment will be done immediately after the baseline assessment to ensure that it is truly random. Patients will be randomly assigned to either experimental group or placebo group with a 1:1 allocation. Randomization will be carried out using online software (Research Randomizer Version 4.0 at https://www.randomizer.org).

Blinding: The study will be conducted as a double-blind trial, meaning that both the participants and the investigators will be unaware of the treatment assignments.

Interventions:

In the experimental group:

Standard symptomatic treatment for itching + Difelikefalin Dose : 0.5 μg per kilogram of weight after each dialysis session.

Duration: 6 wks

In the control group:

Standard symptomatic treatment for itching + Placebo

Duration: 6 wks

Follow-up:

i. At the end 3 wks by- WI-NRS scale,Skindex 10 scale & Adverse events
ii. At the End of 6 wks: WI-NRS scale,Skindex 10 scale & Adverse events

During the 6-week intervention period, patients will report their worst itching intensity using the WI-NRS, and their quality of life will be assessed using the Skindex-10 questionnaire at prespecified follow-up intervals throughout the 6-week period.

Safety will be evaluated by monitoring adverse events, vital signs, clinical laboratory measurements in both group.

5.13. Data analysis:

Data will be entered into an Excel sheet to generate the master sheet. After compelition of data collection, master sheet will be fed into SPSS (Windows version 27.0) for analysis.This study has two types of data: Categorical and quantitative data. Kolmogorov–Smirnov (K-S) test will be used to determine the data distribution. Finding if there is a significant difference between the data, independent samples t-test (or Mann–Whitney test in case of non-parametric data) and Chi-square test for continuous and categorical data, respectively will be used. The difference between the repeated variable in distinct visits using repeated ANOVA with the change from baseline in the weekly mean WI-NRS scale,Skindex 10 Scale. The adjusted mean difference between the groups and its two-sided 95% CI will be presented. A p-value<0.05 will be considered significance.

5.14. Expected outcomes: Difelikefalin will significantly reduce pruritus severity compared to placebo. Participants receiving difelikefalin will report improvements in quality of life and will exhibit a favorable safety profile, with no major adverse events.

5.15. The utilization of results: This trial will provide critical evidence on the effectiveness and safety of difelikefalin in a resource-limited setting, addressing a significant unmet need in the management of CKD-aP. If proven effective, difelikefalin could become a standard treatment option for CKDaP and improve the quality of life for hemodialysis patients in Bangladesh and similar populations globally. Efforts will also be made to present these results at conferences and publish them in peer-reviewed national and international journals. The results and observations of the study will be published as a thesis and submitted to the respective university as a part of the requirement for the MD (Nephrology) Phase B examination purpose. The results of the study will be presented to the Department of Nephrology, CMCH.

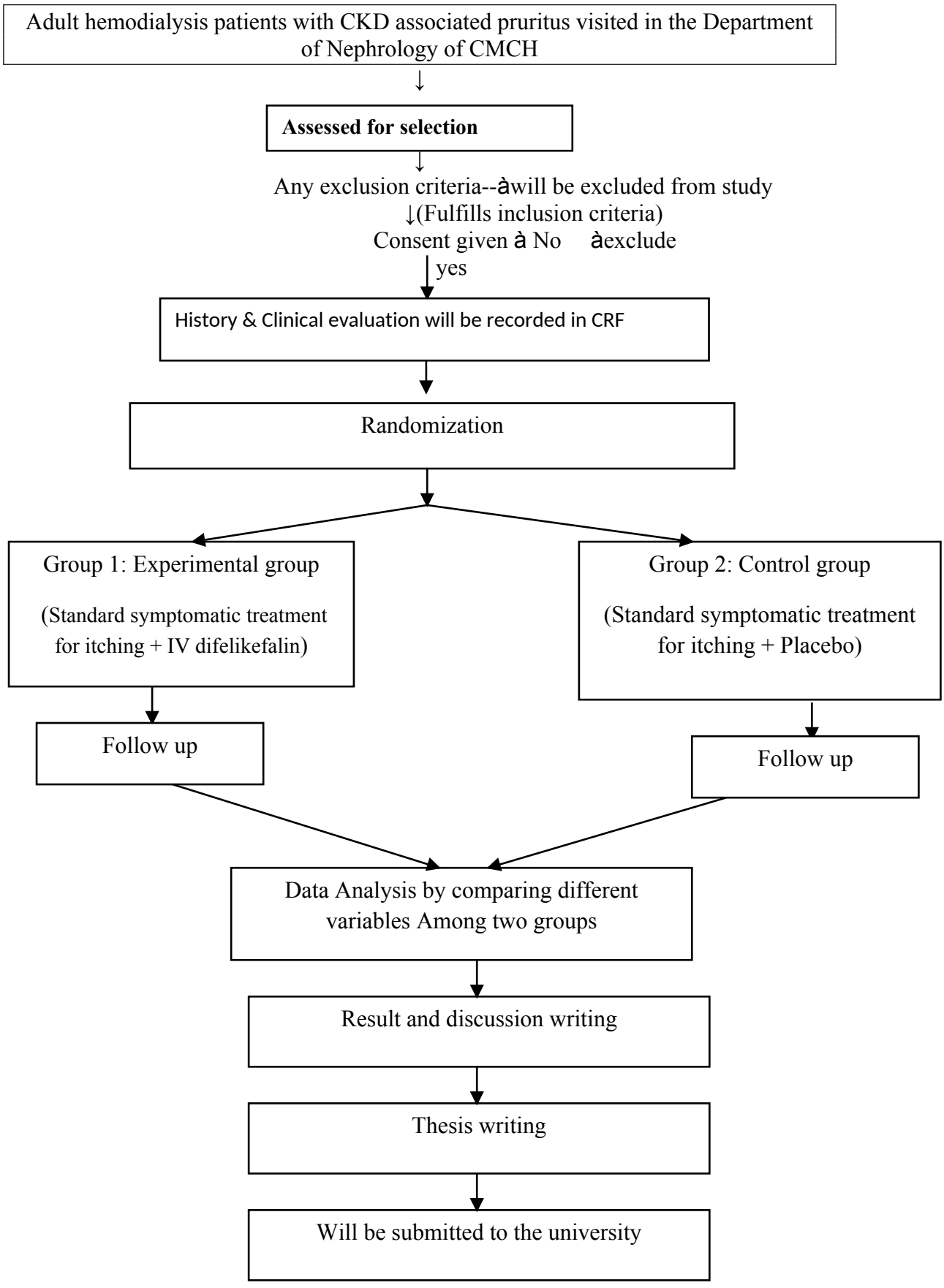
5.16. Ethical implication: Voluntary written consent will be taken from the patient/and legal guardians. All measures will be taken to protect anonymity.The interviews of the patient, clinical examination and investigations will be performed at the respective hospital after explaining the nature and purpose of the study to them, assuring that the information given by them will be used for the interest of the community and that the particulars of the patients will not be disclosed anyway. An independent safety monitoring committee conducted unblinded monitoring of patient safety throughout the trial. The trial protocol will be approved by the Ethical Review Committee of Chittagong Medical College.

Schedule:

Time Schedule (GANTT CHART)

	1st	2nd	3rd	4th	5th -6th	7th -18th	19th - 21th	22th -23th	24th
Problem definition									
Literature review									
Research design									
IRB clearance									
Data collection									
Data analysis									
Report writing									
Submission									

5.17 Study flow chart:



5.18 References:

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Part E

Budget:

Sl. No.	**Head of expense**	
		1st instalment
1	Research tools development	10,000/-
2	Office assistance for organizing the materials	5,000/-
3	Lab Cost	156480/-
4	Drugs	152640/-
5	Report composing	20,000/-
6	Printing	15,000/-
7	Stationaries	5,000/-
8	Data analysis	5000/-
9	Transport/conveyance	1000/-
10	Miscellaneous	5000/-
	Total amount	**3,75,120/-**

Appendix
Case record form

Protocol Title: "Effect of Difelikefalin on CKD-Associated Pruritus in Patients on Maintenance Hemodialysis: A Randomized, Placebo-Controlled Trial"

Patient's identification			
1	Patient ID No.		
2	Patient name :		
3	Adress		
4	Contact no:		
5	Study group	Experimental=1 Control=2	
Demographic characteristics			
1	Age:	……..…years	
2	Sex:	0=Female 1=Male	
Clinical characteristics			
1	Duration of HD	……..Months/years	
2	Duration of pruritus	……..Months/years	
3	Etiology of CKD	1=HTN 2=DM 3=GN 4=Others	
4	Baseline use of antipruritic medication	Anti histamin- Others-	
5	Online Kt/V		
Biochemical			
1	Calcium(mmol/l)		
2	Phosphate(mmol/l)		
3	PTH(pg/ml)		

	Follow-up data	**Baseline**	**At 3-wk**	**At 6-wk**
1	WI-NRS score			
2	Skindex-10 scale total score			

	Adverse Effect		3 weeks	6weeks
1	Nausea	N0= 0 Yes= 1		
2	Vomiting	N0= 0 Yes= 1		
3	Dizziness	N0= 0 Yes= 1		
4	Abdominal pain	N0= 0 Yes= 1		
5	Muscle spasm	N0= 0 Yes= 1		
6	Fall	N0= 0 Yes= 1		
7	Withdrawal	N0= 0 Yes=1		
8	Expired	N0= 0 Yes= 1		
9	Others	N0= 0 Yes= 1		

	Complete the study per the Protocol 0= No 1= yes
	If not reason for drop-out 1. Adverse experience 2. Failure to return for follow-up 3. Patients refuse treatment 4. Patient died 5. Non-co-operation 6.Insufficient therapeutic response

Signature of the researcher: **Signature of the Guide/Co-guide**

A. Worst Itching Intensity Numerical Rating Scale

INSTRUCTIONS

Please indicate the intensity of the **WORST ITCHING** you experienced over the past 24 hours by marking the box with the number that best describes it. After completing the scale below, please provide your initials in the **SUBJECT INITIALS** box indicating that you completed the scale by yourself and the **DATE** and **TIME** you completed the scale.

Worst Itching Over the Past 24 Hours

Please indicate the intensity of the **WORST ITCHING** you experienced over the past 24 hours.

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
NO ITCHING										**WORST ITCHING IMAGINABLE**

B. Skindex-10 Scale

INSTRUCTIONS: During the past **WEEK**, how often have you been bothered by:							
	0 (Never bothered)	**1**	**2**	**3**	**4**	**5**	**6** (Always bothered)
1. Your itching	☐	☐	☐	☐	☐	☐	☐
2. The persistence/reoccurrence of your itching	☐	☐	☐	☐	☐	☐	☐
3. The appearance of your skin from scratching	☐	☐	☐	☐	☐	☐	☐
4. Frustration about your itching	☐	☐	☐	☐	☐	☐	☐
5. Being annoyed about your itching	☐	☐	☐	☐	☐	☐	☐
6. Feeling depressed about your itching	☐	☐	☐	☐	☐	☐	☐
7. Feeling embarrassed about your itching	☐	☐	☐	☐	☐	☐	☐
8. The effects of your itching on your interactions with others (for example: interactions with family, friends, close relationships, etc.)	☐	☐	☐	☐	☐	☐	☐
9. The effects of your itching on your desire to be with people	☐	☐	☐	☐	☐	☐	☐
10. The effect of your itching making it hard to work or do what you enjoy	☐	☐	☐	☐	☐	☐	☐

INFORMED CONSENT FORM

Department of Nephrology, Chittagong Medical College Hospital, Chattogram, Bangladesh.

ERC Research approval number: _ _ _ _ _ _ _ _ _ _ _ _ _ _

Title of Research :Effect of Difelikefalin on CKD-Associated Pruritus in Patients on Maintenance Hemodialysis: A Randomized, Placebo-Controlled Trial"

Name(s) and affiliation(s) of researcher(s): This research is being conducted by Dr.Md.Shariful Islam Sarker, a MD Phase-B Resident, MD (Nephrology) in the Department of Nephrology, Chittagong Medical College, Chattogram, Bangladesh.

Sponsor(s) of Research: This research is self-sponsored

Purpose(s) of Research: The broad aim of this research is to determine whether therapeutic effects of treatment with **Difelikefalin**is better than treatment with **placebo** in patients suffering from **pruritus in hemodialysis patients with chronic kidney disease**.

Procedure for the Research, what shall be required of each participant and the approximate total number of participants that would be involved in the research: Using a block randomization technique, 102 patients will be grouped by the researcher into two equal group 51 patients in Experimental Groups (that will receive **Difelikefalin**) and 51 patients in Control Group (that will receive matched placebo). The symptomatic improvement and quality of life will be studied till 6 weeks.

Expected duration of research and participant(s) involvement: You will be involved in the research till 6 weeks from the enrollment.

Risk(s):.The risk or disadvantage to taking part in this study may be the exposure to the common side effect of **Difelikefalin are** diarrhea, nausea.Dizziness, problems with walking., falling, headache.drowsiness., sudden changes in mental status. However, if any adverse events occur, we will manage the conditions as per guideline

Costs to the participants, if any, of joining the research: You will not require to pay for the drugs, or any related procedure related to the research.

Benefits(s): The finding from this research will help in the management of patients with**pruritus in hemodialysis patients with chronic kidney disease**in the future.

Confidentiality: All information obtained from participants involved in this research will be coded and personal details will be anonymize.

Voluntariness: Your participant in this research is entirely voluntary. You are free to withdraw your consent at any time during the research. It will not in any way influence the way and manner your condition will be managed.

Alternatives to participation: If you choose not to participate, this will not affect you in any way. You will still have treatment in the routine way and at the usual manner.

Due inducements: No patient will be induced to participate in this research.

Consequences of participants' decision to withdraw from research and procedure for orderly termination of participation: If you decide to withdraw from the research after you have initially consented, it will have no bearing on the modality of managing your conditions at the hospital. The attending physicians will attend to you in the standard way without any discrimination.

Modality of providing treatments and action(s) to be taken in case of injury or adverse event(s): There is no expected serious injury or adverse effects other than the recognized adverse events of the investigating drug. Nevertheless, if any such condition arises it will be managed entirely free of cost.

What happens to research participants and communities when the research is over: The research participants and the community will be informed about the research findings through scientific publications. Any of the research participants willing to obtain any non-confidential information about the research will also be obliged.

Statement about sharing of benefits among researchers and whether this includes or excludes research participants: No direct benefit will be shared among researchers.

Any apparent or potential conflict of interest: No conflict of interest is declared.

Statement of person obtaining informed consent: I have fully explained this research to and have given sufficient information, including the risks and benefits, to guide him to make an informed decision.

DATE:_____/_____/_____

SIGNATURE:_____

NAME:

_____

_

Statement of person giving informed consent: The purpose of this research has been explained to me in details. I consent to taking part know that I will be treated either by **Difelikefalin** or placebo for my itching. The risks have been explained to me in details. My participant is entirely voluntary. I understand that am free to withdraw my participant at any time. If I withdraw my participation, it will not alter the standard of my care. All information provided by me will be anonymized and kept in confidence.

DATE:____/____/_____ SIGNATURE/THUMB PRINT: _____

SERIAL NUMBER: _ _ _ _ _ _ _ _ _

WITNESS' SIGNATURE (if applicable): _____

WITNESS' NAME (if applicable): _____

Detailed contact information including contact address, telephone, e-mail and any other contact information of researcher(s), instructional ERC and head of the institution: This research has been approved by the Ethical Review Committee of Chittagong Medical College and they can be contacted at the College Building, Chittagong Medical College. Also, if you have any question about your participation in this research, you can contact the researcher, Name: Dr.Md.Shariful Islam Sarker, MD Phase-B Resident, MD (Nephrology) in the Department of Nephrology, Chittagong Medical College, Chattogram, Bangladesh.

Cell No: 01738647201

Email:sobujshariful@gmail.com

Consent Form

"Effect of Difelikefalin on CKD-Associated Pruritus in Patients on Maintenance Hemodialysis: A Randomized, Placebo-Controlled Trial"

After being fully informed about the objectives, consequences of the study, and any right to withdraw myself from the study at any time for any purpose whatsoever, I am…….
Here by giving consent to participate in the study conducted by **Dr. Md.Shariful Islam Sarker** (Nephrology), Phase B student, CMCH.
I fully recognize that my participation in this study will generate valuable medical information that might be used for the interest of patients in the future.
In this research, if any adverse effects of drugs are found, investigators will take immediate measures for treatment.
I shall try my best to comply with the instruction given by the investigator throughout the whole period of study.

Signature/Thumb impression of the patient's guardian	Signature/Thumb impression of the Subject
Date…….	Date…….
Signature of the Investigator	Signature of the Witness
Date…….	Date…….

Data and Safety Monitoring Board

Title: **"Effect of Difelikefalin on CKD-Associated Pruritus in Patients on Maintenance Hemodialysis: A Randomized, Placebo-Controlled Trial"**

Name of the researcher: This study is being conducted by Dr.Md.Shariful Islam Sarker, Phase-B Resident, MD (Nephrology), Department of Nephrology, Chittagong Medical College.

Place of the study: Department of Nephrology, Chittagong Medical College Hospital, Chattogram.

Type of Study: Randomized Controlled Trial

Membersoftheboard:

• ……. Professor, Department of Nephrology Chittagong Medical College and Hospital, Chattogram, Bangladesh

• …… Assistant professor, Department of Medicine, Chittagong Medical College and Hospital, Chattogram, Bangladesh

• …….. Assistant professor, Department of Dermatology, Chittagong Medical College and Hospital, Chattogram, Bangladesh

DATA AND SAFETY MONITORING PLAN

Once a protocol is referred to the data and safety monitoring committee (DSMC). The first steps for the principle investigator to develop a Data and Safety Monitoring Plan (DSMP) A DSMP is a written plan that specifies a system for appropriate study oversight to ensure: (1) safety of clinical research subjects, (2) validity and integrity of research data, and (3) appropriate termination study. Once the plan elements listed here are submitted to the DSMC, the DSMC will work with the investigator to finalize the plan and assure that it is implemented.

Enrollment of the study participants by months:

Month	**Approached**	**Eligible**	**Randomized**	**Withdrawn**	**Actual #**	**Cumulative #**
1						
2						
3						
4						

Subject Status:

Patient ID	**Date enrolled**	**Date completed**	**Status (Active/ completed/Withdrawn)**	**Reason of withdrawal**	**Adherence**	**Intervention duration**
1						
2						
3						
4						

Adverse events (AE) Patient ID

Patient ID	AE Onset	AE End	Severity	Related to intervention	Action taken	Outcome	Comment
1							
2							
3							
4							

Appendix

Withdrawal Form

I. ..... myself thesis case no..... of Dr.Md.Shariful Islam Sarker Hereby I withdraw myself/ my patient from signed protocol of treatment. I will continue the treatment of myself/my patient according to standard protocol

Name.....Signature/Thumb Impression:

Name of Witness: .....Signature/Thumb Impression: .....

Date: .....

Name & Signature of researcher.....