CLINICAL RESEARCH SUPPORTING UNIT
Faculty of Medicine, Universitas Indonesia
Jl. Salemba Raya 4, Jakarta 10430 Telp/Fax (021) 391 0552

CONFIDENTIAL

CLINICAL TRIAL PROTOCOL

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Efficacy and Safety of PEG 3350 for Treatment of Chronic Constipation

Principal Investigator	: Prof. Dr. dr. Murdani Abdullah, SpPD-KGEH
Co-Investigators	: dr. Amanda Pitarini Utari, SpPD dr. Saskia Aziza Nursyirwan, SpPD dr. Rabbinu Rangga Pribadi, SpPD dr. Virly Nanda Muzelina, SpPD
Trial Coordinator	: Prof. Arini Setiawati, PhD
Trial Monitor	: dr. Taruna Dibya
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Under contract No.	:
Director	: Masanobu Sato
Address	: Jl. Tanah Abang II No. 4, Jakarta Pusat, Indonesia

Name	Phone/Fax/e-mail	Address
Principal Investigator : Prof. Dr. dr. Murdani Abdullah, SpPD-KGEH	Email : murdani08@gmail.com Hp: 0812-9550-812 Office: 021-3153957 ext 6704	Departemen Gastroenterologi RSCM, Jl. Diponegoro no. 71, Jakarta
Co-Investigators : dr. Amanda Pitarini Utari, SpPD dr. Saskia Aziza Nursyirwan, SpPD dr. Rabbinu Rangga Pribadi, SpPD dr. Virly Nanda Muzelina, SpPD	Office: 021-3142454 ext 6704	Departemen Gastroenterologi RSCM, Jl. Diponegoro no. 71, Jakarta
Study Monitor : dr. Taruna Dibya	Email: tarunadibya@gmail.com Phone: 0812-1160-3275	Clinical Research Supporting Unit (CRSU) FKUI IMERI FKUI, Tower A lt. 11 Jl. Salemba Raya 6, Jakarta

Efficacy and Safety of PEG 3350 for Treatment of Chronic Constipation

Prof. Dr. dr. Murdani Abdullah, SpPD-KGEH _____
Principal Investigator Date:

Dr. dr. Evy Yunihastuti, SpPD, K-AI _____
Study Coordinator RSCM-FMUI Date:

Prof. Dr. dr. Dadang Makmun, SpPD, KGEH _____
Head of Gastroenterology Division RSCM Date:

Prof. dr. Frans. D. Suyatna, PhD, SpFK _____
Head of CRSU FMUI Date:

Prof. Arini Setiawati, PhD _____
Clinical Trial Coordinator CRSU FMUI Date:

Masanobu Sato _____

(PT. Meiji Indonesia) Date:

Efficacy and Safety of PEG 3350 for Treatment of Chronic Constipation

1. Introduction

Polyethylene (PEG) 3350 is a mixture of non-absorbable, non-metabolized polymers of mean molecular weight (MW) 3350 (± 10%) that act as pure osmotic agents. It contains no more than 0.1% of lower MW PEGs that are absorbable and excreted unchanged by glomerular filtration.

Low dose PEG has been shown to be effective for treatment of chronic constipation. Ingestion of a solution containing PEG 3350 at low doses for 8 days significantly increased stool weight. The volume of water taken with PEG did not modify the results.

The osmotic agent lactulose is a synthetic disaccharide that is not absorbed by the small intestine but is readily metabolized by colonic bacteria. It has been shown to be effective for treating constipation, especially in the elderly. Intracolonic fermentation of lactulose is associated with production of gases and with colic, bloating, and flatulence. Furthermore, chronic ingestion of lactulose may induce changes in colonic bacterial metabolism and reduced efficacy in the treatment of chronic constipation. Therefore, in the present study, lactulose is used as comparator in short-term only[1].

Whereas PEG is osmotically active without causing colonic gas production, and it has been shown to be nontoxic and can be ingested in large quantities without harmful effect.

2. Study objective

To determine the efficacy and safety of PEG 3350 for short-term treatment of chronic constipation in adults.

3. Study design

- Parallel group design, randomized, open-label, versus comparator for 14 days.
- Block randomization using random permutation blocks of size 4.
- Blinded evaluation.

4. Patients

4.1. Inclusion criteria

a. Males and females aged ≥ 18 years.
b. BMI ≥ 18.5
c. Organic bowel disease will be ruled out by Fecal Immunochemical Test (FIT) and/or colonoscopy.
d. Must have ≤ 2 bowel movements during a 7-day qualification period.
e. In otherwise good health as judged by a physical examination and laboratory testing.

f. Not taking medications known to affect bowel function in one week before study.
g. Willing to participate in the study by signing the informed consent.

4.2. Exclusion criteria

a. Hypersensitive to the study medication.
b. obstructive ileus.
c. IBS and/or IBD

5. Study drugs

5.1. Drug presentation

- Test drug: PEG 3350 17 g powder per sachet
- Comparator: Lactulax syrup 15 ml (containing 10 g of lactulose)

5.2. Drug administration

- The content of each sachet of PEG is dissolved in 240 mL of water, drink it once daily at bedtime, for a duration of 14 days.
- 15 ml of Lactulax syrup is drunk with 240 ml of water once daily at bedtime, for a duration of 14 days.

5.3. Drug supply, packaging and labelling

a. PEG 3350 and Lactulax syrup will be supplied by PT. Meiji Indonesia.
b. CRSU FMUI will package PEG sachet and Lactulax syrup for individual patient according to a pre-determined randomization list. Each drug package is labelled with the patient randomization number and dosage instruction. Each patient will receive drug supply for consumption at day 0 and day 7 (for 7 days each) plus a few days in excess, for compliance check and to allow additional days for patient visit.
c. Each patient receives:
    - Each patient receives a diary book at day -7
    - For 7-day Treatment of Period 1 and 7-day Treatment of Period 2:
      10 sachets of PEG 3350 or Lactulax syrup 1 bottle of 120 ml:
        - Dissolve content of 1 sachet of PEG in 240 mL of water, drink once daily at bedtime, or
        - 15 ml of Lactulax syrup, drink with 240 ml of water once daily at bedtime.
    - Study patients are instructed not to take any other laxative.

5.4. Drug accountability

The investigators will be responsible for recording the receipt of study drugs from the Sponsor, dispensing the study drugs to each patient, and return of all unused drugs to the Sponsor. Any unused drug should be returned to the sponsor at the conclusion of the study. Forms will be made available.

5.5. Drug storage

The investigators are responsible for assuring that the study drugs are stored in a secure, limited access area, protected from extremes of light, temperature, and humidity.

6. Concomitant medication

None

7. Endpoints measured (by blinded evaluator)

7.1. For efficacy: study patients are provided with diaries to record each bowel movement and associated symptoms.

a. Primary endpoint: number of bowel movements (defecation) per 7-day period.

b. Secondary endpoint:

- Symptom scores:
  - Stool consistency: 0 = hard, 1 = firm, 2 = soft, 3 = loose, 4 = watery (by anamnesis - visual comparison)
  - Stool passage: 0 = strain, 1 = easy, 2 = loss of control (by anamnesis)
  - Cramping and rectal irritation associated with each bowel movement: 0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = have to discontinue (by anamnesis)
  - Flatus: 0 = none, 1 = moderate, 2 = occasional, 3 = frequent, 4 = very frequent
- Overall rating of effectiveness: effective / not effective.

  Effective: patients with ≥ 3 bowel movements per 7-day period.

7.2 For safety

a. AEs – total and related (ADRs)

b. SAEs – total and related (SADRs)

8. Sample size

Based on number of bowel movements / week:

Number of bowel movements caused by PEG 3350 at week 2 = 4.5 $\pm$ 3.0[2]

If PEG 3350 is considered non-inferior to the comparator lactulose, then the difference (Δ) is assumed to be a maximum of 10% = 0.45.

Non inferiority margin = 1

α = 5% (1-sided) → Z_α = 1.645

β = 10% (1-sided) → Z_β = 1.282

$$n_1 = n_2 = \frac{2SD^2(Z_\alpha + Z_\beta)^2}{(margin + \Delta)^2}$$

$$= \frac{2x3x3\,(1.645 + 1.282)^2}{(1 + 0.45)^2}$$

$$= \frac{18\,x\,8.567}{2.1025} = \frac{154.206}{2.1025} = 73.34 \rightarrow 74$$

20% DO → 1.25 x 73.34 = 92

Total = 2 x 92 = 184 patients

9. Evaluation chart

Time Schedule of Evaluation

	Screening	Baseline	Treatment Period 1	Treatment Period 2	After Treatment
Day	-7	0	7	14	21
Visit	1	2	3	4	5
Informed consent	√				
Demography	√				
Medical history	√				
Physical examination	√				
Laboratory tests: – Routine hematology – Liver & kidney function	 √ √			 √ √	
Urinalysis	√			√	
Stool test	√				
Colonoscopy PA colonoscopy	√				
Inclusion/exclusion criteria		√			
Study drug dispensed		√	√		
Collect unused study drug		√	√	√	
Patient diary given Record: –Number of bowel movement (BM) –Stool consistency –Stool passage –Cramping & rectal irritation –Flatus → assoc. with each BM	√	√	√	√	
Patients diary reviewed		√	√	√	√
Overall rating of effectiveness				√	
Adverse events		√	√	√	√
Patient status				√	

10. Patient discontinuation

10.1. Reasons for discontinuation

a. At the request of the patient.

b. If a patient undergoes an acute medical condition requiring intensive treatment, the patient will be withdrawn from the study.

c. If the investigator considers that a patient's health be compromised due to adverse effects that occur during the study.

d. If the patient does not comply with the investigator's instructions.

10.2. Data collected for discontinued patients

a. Complete all examinations at the current visit.

b. Complete the CRF with:
- the time, date and reasons for discontinuation;
- assessment of efficacy and safety of the assigned drug until the last day.

c. If necessary, arrange alternative medical care for the discontinued patient, and record in the CRF any follow-up of patients who are discontinued due to adverse events.

10.3. Unevaluable criteria

Patients who are recognized after entry to be uneligible (do not meet selection criteria).

11. Safety assessments

All adverse events will be recorded in the CRF: the onset date, the date resolved/ongoing, the severity (mild, moderate, severe), the effect on study drug dosing (reduced, interrupted, or discontinued), and the outcome/action taken (additional therapy, hospitalization, additional study visit, etc.). The relationship with study drug will also be assessed and categorized as probable, possible, or unlikely.

In order to detect all possible adverse events, questions to the patient should not be restricted to "How have you been feeling after the last dose?" or some similar general question, but some questions should also be directed to the known adverse reactions of the test drug.

If a serious event occurs, the investigator must report it immediately (within 24 hours) by telephone to the Trial Monitor,

Name of the Trial Monitor : dr. Taruna Dibya
Address : Clinical Research Supporting Unit, Faculty of Medicine, Universitas Indonesia
Jl. Salemba Raya 6, Jakarta 10430.
Phone : (021) 291 891 60

and within 3 calendar days to the Ethics Committee regardless of treatment group or whether any relationship to drug is suspected.

Serious adverse events include events which:

- are fatal
- are life-threatening or potentially life-threatening
- result in permanent disability
- require hospitalization or prolongation of a hospital stay
- involve cancer, a congenital anomaly, or the result of a drug overdose
- suggest significant hazard to the patient

Any death during or within a reasonable period after a study must be reported as a serious event, independent of the circumstances or suspected cause. In such a case, a summary of available autopsy findings must be submitted as soon as possible to the Trial Monitor.

An intercurrent illness should also be reported immediately if regarded as serious according to the above criteria.

It should be emphasized that, regardless of the above criteria, any additional adverse events which the investigator considers significant should be immediately reported.

In case a female patient becomes pregnant during the study, this event should also be reported within 24 hours by telephone to the Trial Monitor.

Any event that should be immediately reported are described in detail on a special Adverse Event Reporting Form with the assistance of the Trial Monitor. This special form will be made available by the sponsor. This detailed SAE Report should be submitted within 15 calendar days to the Sponsor and the Ethics Committee.

The drug-related SAEs should be submitted to the NRA within 15 calendar days.

12. Study management

12.1. Study completion (PLEASE, WRITE CLEARLY !)

The investigators will ensure that all observations and findings on each patient are transcribed from primary source data correctly and completely in the CRFs using black ballpoint pen.

All corrections on a CRF must be made in a way which does not obscure the original entry (do not use eraser or tipp-ex, but cross with only one line). The correct data must be inserted, initialled and dated by the investigator.

The summary page of the CRF must be signed by the principal investigator, thereby stating that he/she takes responsibility for the accuracy of the data in the entire CRF.

12.2. Study monitoring

The Trial Monitor will visit the investigators periodically to assess the progress of the study and the adherence to the protocol. The investigator should allow the Trial Monitor to visit and check the CRF for completeness and accuracy.

The Trial Monitor should report all irregularities found, to the Sponsor and Trial Coordinator in the Clinical Research Supporting Unit Faculty of Medicine, Universitas Indonesia, so that corrective measures can be taken.

The investigators should keep source documents such as:

- medical record (complete history and physical examination, treatment given and results)
- laboratory reports
- any consultation reports
- etc.

for possible review by the Trial Monitor.

12.3. Retention and disclosure of data

a. The trial data must be retained until at least 2 years after the last approval of a marketing application in the region.

b. All information obtained from the study will be regarded as confidential, at least until the study results have been published.
If any information relative to this study will be disclosed to a third party, permission from the investigators and sponsor is necessary.

13. Study Procedure

All 184 patients will be collected from Petamburan community, Paseban community and RSUPN dr. Cipto Mangunkusumo.

After signing the informed consent, the study candidates will be evaluated for enrollment: history of constipation, hypersensitivity to the study medication, demographics, organic bowel disease checking by FIT and/or colonoscopy, IBD, IBS, serum chemistry tests and urinalysis. Then, 7-day qualification period, before which candidates will receive one diary book to record how many times defecation during these 7 days. Candidates with one or two bowel movement (defecation) during these 7 days will continue into the treatment phase.

Each patient will receive 10 sachets of PEG or 1 bottle of 120 ml Lactulax syrup. The content of each PEG sachet will be dissolved in 240 ml of water and drink it once daily at bedtime for 7 days or 15 ml of Lactulax syrup, drink with 240 ml of water once daily at bedtime for 7 days. During these 7 days, the stool consistency (hard, firm, soft, loose or watery) is compared with pictures provided, the stool passage (strain, easy or loss of control), and the following symptoms: cramping, rectal irritation, and flatus associated with each bowel movement, will be recorded in the diary book.

After 1 week, the patient will return to the study site to return the unused drug and to show the dairy book. The investigator will examine the dairy book to look for any improvement of the constipation. The patient will again receive 10 sachets of PEG or 1 bottle of 120 ml Lactulax syrup for another week, and return at the end of the second week, bringing the unused drug and the dairy book to the investigator.

The patients will be visited by the co-investigator on day 21 (no drug being administered during this last week), the intention is to have information whether any adverse event occurs during this week.

14. Data analyses

14.1. Efficacy analysis

After parallel-group design (at 7 and 14 days):

Statistical analysis between PEG vs. Lactulose:

- bowel movements frequency: use unpaired t-test or Mann-Whitney test
- symptom scores: use Mann-Whitney test
- overall rating of effectiveness: use X^2 test

14.2. Safety analysis

After double-blind cross-over design: all patients who take at least one dose of the study drug and return at least once post-randomization, will be subject to safety analysis.

a. Adverse events (AEs)

All adverse events will be listed per group (PEG and comparator drug), both the incidence and the percentage. No statistical test will be used for comparison.

b. Adverse drug reactions (ADRs)

The adverse events with possible and probable relationship to the study drug (ADRs) will also be listed as the incidence and the percentage per group (PEG and comparator drug). No statistical test will be used.

15. Publication

Publication of the trial will be done after agreement of all parties and is the responsibility of the Principal Investigator, assisted by the Trial Coordinator in Clinical Research Supporting Unit, FMUI.

16. Ethical Committee Approval

Approval from the Ethical Committee at the Faculty of Medicine Universitas Indonesia must be obtained before starting the trial.

17. Clinical Trial Registry

Clinical Trial Registry Number will be sought from ClinicalTrials.gov.

18. References

1. A Attar, M Lemann, A Fergusen, M Halphen, M-C Boutron, B Flourie, et al. Comparison of a low dose polyethylene glycol electrolyte solution with lactulose for treatment of chronic constipation. Gut. 1999; 44: 226-30.
2. JA DiPalma, PH DeRidder, RC Orlando, BE Kolts, MvB Cleveland. A randomized, placebo-controlled, multicenter study of the safety and efficacy of a new polyethylene glycol laxative. Am J Gastroenterology. 2000; 95(2): 446-50.
3. JA DiPalma, MvB Cleveland, J McGowan, JL Herrera. An open-label study of chronic polyethylene glycol laxative use in chronic constipation. Aliment Pharmacol Ther. 2006; 25: 703-8.
4. M vB Cleveland, DP Flavin, RA Ruben, RM Epsteins, GE Clark. New polyethylene glycol laxative for treatment of constipation in adults: a randomized, double-blind, placebo-controlled study. South Med J. 2001; 94(5): 478-81.