

Study Title: "A multi-center, open label, randomised, parallel-group study to compare the efficacy of cholestyramine plus standard treatment versus prednisolone plus standard treatment versus standard treatment alone in the treatment of overt hyperthyroidism"

Clinical study protocol number/version: 3.0

Development phase: Phase III

Study initiation date: May 2017 or upon approval from MREC

Study completion date: 31st December 2017

Date of protocol : 5th June 2017 Version 3.0

Amendment number(s) and date : Ammendment No. 1 (3rd May 2017)

Ammendment No. 2 (5th June 2017)

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| Date: 7 th March 2017 | Date: |

This protocol incorporates the following amendment(s):

| Amendment No. | Date of Amendment | Initials of CRC coordinator |
|----------------------|---------------------------|------------------------------------|
| 1 | 3 rd May 2017 | |
| 2 | 5 th June 2017 | |
| | | |

Confidentiality Statement

May not be used, divulged, published or otherwise disclosed without the written consent of the primary investigator.

1 SYNOPSIS

Title of study: "A multi-center, open label, randomised, parallel-group study to compare the efficacy of cholestyramine plus standard treatment versus prednisolone plus standard treatment versus standard treatment alone in the treatment of overt hyperthyroidism"

Sponsor: Ministry of Health, Malaysia

Clinical Phase: III

Investigators:

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-

Study period: One year

Planned date of first subject enrolment: May 2017 or upon obtaining approval from MREC

Planned date of last subject completed: 31st December 2017

Objectives:

Primary objective:

1. To assess the efficacy between Cholestyramine plus Standard treatment (Carbimazole plus Propranolol), Prednisolone plus Standard treatment and Standard treatment alone in subjects with overt hyperthyroidism

Secondary objective:

1. To assess the safety profile of Cholestyramine plus standard treatment, Prednisolone plus standard treatment and standard treatment alone.
-

Methodology:

This is a randomised, open label, controlled, parallel group with allocation ratio 1:1:1 design

Number of patients:

It is planned to randomise an estimated total of 135 adult patients with overt hyperthyroidism into this study, with 45 patients randomised into each treatment group.

Number of centres: 3

Inclusion criteria:

1. Subject is > 18 years of age at initial screening visit
 2. Subject has signed and dated Informed Consent form
 3. Subject with moderate to severe overt hyperthyroidism (defined as FT₄ > 1.5 times upper limit of normal) caused by Graves' disease
 4. Women of childbearing potential can be included if surgically sterile or using double contraception with at least one method being barrier contraception
-

Exclusion criteria:

1. Inability or unwillingness to provide written consent
 2. Inability or unwillingness to comply with the requirements of the protocol as determined by the investigator
 3. Pregnancy, breastfeeding or use of non-reliable method of contraception
 4. Subjects with history of chronic liver disease, chronic renal failure, heart failure, diabetes mellitus
 5. Previous history of hypersensitivity to cholestyramine
 6. Subjects with complete biliary obstruction, intestinal obstruction
 7. Previous history of hypersensitivity to prednisolone or other steroid compound
 8. Subjects with underlying infection (systemic fungal, tuberculosis, bacterial, malaria, viral hepatitis, ocular herpes simplex, HIV)
 9. Subjects with psychiatric disorder
 10. Subjects with gastrointestinal diseases (diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, ulcerative colitis, abscess or other pyogenic infection)
 11. Subjects with ocular disease (cataract, glaucoma)
 12. Subjects with osteoporosis or osteoporotic fracture
 13. Participation in another clinical trial/ receipt of investigational drug within 4 weeks prior to screening visit
 14. Current use of cholestyramine or other bile acid resins (colestipol, colesevelam)
 15. Current use of prednisolone or other steroid compound (hydrocortisone, dexamethasone)
 16. Subjects with history of bronchial asthma, bronchospasm, peripheral vascular disease or adverse reactions to propranolol
 17. Subjects with adverse reactions to carbimazole such as agranulocytosis, severe skin rash
 18. Hypokalemia (Serum $K^+ < 3.5\text{mmol/L}$)
 19. Thyroid storm defined as Burch Wartofsky score of >45
-

Test treatment, dose and mode of administration:

There are 3 treatment groups:

Group 1: Cholestyramine plus standard treatment

Group 2: Prednisolone plus standard treatment

Group 3: Standard Treatment only

Standard treatment consists of Tablet Carbimazole 30 mg daily and Tablet Propranolol 40 mg twice daily. The duration of treatment for each group will be 4 weeks.

| |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Group 1: Cholestyramine plus standard treatment |
| Cholestyramine powder 4g twice daily, Tablet Carbimazole 30 mg daily, Tablet Propranolol 40 mg twice daily. |
| Group 2: Prednisolone plus standard treatment |
| Tablet Prednisolone 30 mg daily for week 1, 20 mg daily for week 2, 10 mg daily for week 3 and 5 mg daily for week 4, Tablet Carbimazole 30 mg daily, Tablet Propranolol 40 mg twice daily |
| Group 3: Standard Treatment only |
| Tablet Carbimazole 30 mg daily, Tablet Propranolol 40 mg twice daily |

Duration of treatment with study medication:

4 weeks

Criteria for evaluation:

1. Efficacy endpoint(s)

- Primary endpoint

1. Proportion of subjects with normal thyroid hormone levels (Defined

as serum free T₄ or serum free T₃ levels) measured at 2 and 4 weeks after initiation of study treatment.

2. Safety endpoints

- Number of subjects with adverse effects during the intervention and follow up period (total duration 6 weeks)
- Number of subjects with serious adverse events during intervention and follow up period (total duration 6 weeks)

Statistical methods:

1. For primary objectives, all comparisons of means between treatment will be analysed using one-way ANOVA and all pairwise comparisons of proportions between treatments will be analysed using two-sided Z test. Analyses will be based on intention-to-treat and per protocol analysis.
2. For secondary objectives, all comparisons of means between treatment will be analysed using one-way ANOVA and all comparisons of proportions will be analysed using chi-square test of independence. Analyses will be based on safety set analysis.

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3 LIST OF ABBREVIATIONS

| | |
|-----------------|---------------------------------------|
| ⁰ C | Degree Centigrade |
| AE | Adverse event |
| ATD | Anti thyroid drug |
| BD | Twice daily dose |
| BP | Blood pressure |
| CRF | Case report form |
| CV | Curriculum vitae |
| FPG | Fasting plasma glucose |
| FT ₄ | Free T ₄ |
| FT ₃ | Free T ₃ |
| GCP | Good clinical practice |
| HR | Heart rate |
| ID | Identification |
| mmHg | Millimetre mercury |
| MREC | Medical Research and Ethics Committee |
| OD | Daily dose |
| RPG | Random plasma glucose |
| RAI | Radioactive iodine |
| SAE | Serious adverse event |
| TDS | Three times a day dose |
| TSH | Thyroid stimulating hormone |
| TRAb | Thyroid stimulating receptor antibody |
| LFT | Liver function test |
| RFT | Renal function test |

4 GLOSSARY OF TERMS

| | |
|--------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Eligible | Qualified for enrolment into the study based on strict adherence to inclusion and exclusion criteria |
| Investigator | Treating physician |
| Subject(s) | Individuals enrolled in the clinical study |
| Diabetes | Fasting plasma glucose more ≥ 7 mmol/L or Random plasma glucose ≥ 11.1 mmol/L |
| Hypokalemia | Serum potassium (K^+) < 3.5 mmol/L |
| New onset sepsis | Defined as new onset life-threatening organ dysfunction caused by a dysregulated host response to infection. |
| Hypothyroid | Symptoms of hypothyroidism coupled with biochemical Free T_4 normal or below lower limit of reference range and TSH above upper limit of reference range |
| Drug hypersensitivity Reaction | An immune mediated reaction to a drug and manifests as mild to severe skin rash, anaphylaxis or serum sickness |
| Hospitalisation | An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility |
| All-cause mortality | An event that results in death of a subject |
| Constipation | Fewer than 3 bowel movements a week |
| Diarrhea | Abrupt onset of 3 or more loose stools per day |

5 ETHICS & REGULATORY CONSIDERATIONS

5.1 Independent Ethics Committee

The study protocol and any other documents including the Patient Information Sheet, Consent Form, subject requirement procedures and advertisements to be used, and information on payments and compensation available to subjects, will be submitted to MREC. The study will be started only after receiving MREC approval. MREC approval will be requested if there is any amendment to the protocol, other than administrative ones.

The following will be informed to the MREC:

- Any amendment to the protocol, informed consent changes or revisions of other documents originally submitted for review.
- Any serious and/or unexpected events occurring during the study, where required.
- Any new information that may adversely affect the safety of the subjects or the conduct of the study.
- An annual update on the progress of the study and/or request for re-approval, where required.
- Final study report when the study has been completed, where required.

All correspondence with the MREC will be filed in the Investigator's Study File.

5.2 Ethical conduct of the study

The study will be conducted in compliance with the protocol. These are designed to ensure adherence to the ethical principles that have their origin in the "World Medical Association Declaration of Helsinki" (see Appendix), "Malaysian Guidelines for Good Clinical Practice" and applicable regulatory Requirements.

5.3 Informed consent and subject information

The written, informed consent will be obtained from every subject prior to participation in this study by the research investigator. This is following the

subject's complete understanding of the study. The investigator will inform every subject in detail about the nature of the study, its purpose, the treatments and the probability of random assignment to treatment groups, those aspects of the study that are experimental, the procedures involved including all invasive procedures and the discomfort they may entail, the possible risks including to an embryo, foetus or nursing infant where applicable, the reasonably expected benefits the expected duration and the approximate number of subjects involved and the subject's responsibilities.

Study subjects will also be informed that:

- Participation in this study is voluntary and that he/she may withdraw from this study at any time for any reason and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.
- Alternative procedures or treatments that may be available and the important potential benefits and risks of these available alternative procedures or treatments.
- Any compensation for additional costs and/or injury caused to a subject attributable to participation in the study.
- Any foreseeable circumstances and/or reasons under which the subject's participation in the study may be terminated.
- Subject will be provided the Investigator's contact details for further information regarding the study and who to contact in the event of study related injury.

Written consent will be obtained from each subject involved in the study. If written consent is not possible, oral consent can be obtained if witnessed by a signed statement from one or more persons not involved in the study, stating why the patient was unable to sign the consent form. The informed consent form used to document written or oral consent in the study must be received prior to approval from the MREC. If the subject and his/her parent/guardian are unable to read, the investigator or designee will explain to the subject the content of the Patient Information Sheet and Consent Form point by point in the presence of an impartial witness. The witness will personally sign and date the consent form. The potential

study subject and/or his/her parent/guardian should be given the opportunity to ask questions and time for consideration.

A copy of the Patient Information Sheet and signed Consent Form should be given to the subject. The original document must be filed by the principal investigator in the Investigator's Study File. A sample of the Patient Information Sheet and Consent Form can be found in the Appendix of this protocol

Study subjects may have the right to access, and make a copy of their medical and/or clinical study records as allowed by applicable privacy laws. Subjects may ask to see their records by requesting such records from the study doctor or the facilities where the study is being conducted. However, to ensure the valid results of the study, subjects may not be able to review or make a copy of some of the records related to the study until after the study has been completed.

5.4 *Patient protection procedures*

5.4.1 *Procedures in the event of Emergency*

All appropriate measures will be taken to ensure the safety of the patients, including referral to a specialist if needed. There will be follow up of the outcome of any adverse events (clinical signs, laboratory values or other, etc.) until the return to normal or stabilization of the patient's condition. In the case of any serious adverse event, the patient will be followed up until clinical recovery is complete and laboratory results have returned to normal, or until progression. In the event of emergency, subjects will be instructed to proceed to the nearest emergency department and notify the investigator immediately. An emergency may constitute an SAE.

5.4.2 *Procedures in the event of Pregnancy*

The subject will be instructed to inform the investigator if she becomes pregnant during the study and seek advice regarding continuation of the study treatment. The investigator will follow up the pregnancy until the outcome is known.

5.4.3 *Patient data protection*

The investigator will assure that the subjects' anonymity will be maintained and that the confidentiality of records and documents that could identify subjects will be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements.

- Subjects will be identified only by their assigned identification number and initial on all CRFs and other records and documents submitted
- The investigator will keep a Patient Identification List with complete identification information (name, address, contact number, IC#) on each subject.
- Documents that are not for submission such as subject's written informed consent form, should be maintained by the investigator in strict confidence.

Representatives of MREC or other regulatory agencies will be granted direct access to subject medical records and other study documents for verification of study procedures and data without violating the confidentiality of the subject. The subject should be informed that by signing a written informed consent form, the subject or his/parent or guardian is authorizing such access.

All electronic data processed will be identified by patient numbers only, thereby ensuring that patients' identity remains unknown.

5.4.4 Insurance

With respect to any liability directly or indirectly caused by the investigational products in connection with this study, the sponsor assumes liability by law on behalf of the investigator and his/her staff for possible injury to the subject, provided the investigator and his/her staff have followed the instructions of the sponsor in accordance with this protocol and any amendments thereto, that the investigational products administered to the subject in this study have been supplied by the sponsor and that the investigator and his/her staff have in general performed this study in accordance with scientific practice and currently acceptable techniques and know how.

6 INTRODUCTION AND BACKGROUND

Hyperthyroidism is the second most common endocrine disorder in the world with an estimate prevalence rate of 0.5-1.3%^{2,3}. Its incidence is 0.4 per 1000 women and 0.1 per 1000 men. Graves' disease is the commonest cause of hyperthyroidism followed by toxic multinodular goiter, toxic adenoma and thyroiditis.

Hyperthyroidism is diagnosed clinically and biochemically with typical signs and symptoms of hyperactivity, irritability, heat intolerance, sweating, palpitations, fatigue, weakness and weight loss with normal or increased appetite. The 2016 American Thyroid Association (ATA) Guidelines for Diagnosis and Management of Hyperthyroidism and other causes of Thyrotoxicosis have defined overt hyperthyroidism as elevated serum free T₄ (FT₄) and/or total T₃ (TT₃) and low serum TSH (usually <0.01mU/L). The ATA taskforce has recommended a rough guide to methimazole dosing based on the biochemical severity of hyperthyroidism, classified as mild (FT₄ levels 1-1.5 times upper limit of normal), moderate (FT₄ 1.5-2 times the upper limit of normal and severe (FT₄ approximately 2 to 3 times upper limit of normal) ⁴.

Elevated thyroid hormones have profound effects on almost every tissue and organ system. Uncontrolled hyperthyroidism results in increase cardiovascular morbidity and mortality primarily due to heart failure and thromboembolism. About 6% of thyrotoxic patients develop symptoms of heart failure secondary to tachycardia-mediated mechanism and isolated right sided heart failure as a result of pulmonary artery hypertension. Therefore treatment is essential to restore a euthyroid state that will lead to resolution of signs and symptoms of heart failure. Early recognition and prompt treatment can reverse the cardiovascular manifestations thus reducing the risk of developing permanent dilated cardiomyopathy with impaired left ventricular function⁵. Atrial fibrillation occurs in 10-20% of patients with hyperthyroidism, more commonly in older patients. In several studies 10 to 40% of patients with hyperthyroidism and atrial fibrillation had an arterial embolus resulting in a higher risk of thromboembolic stroke⁶. Studies have also shown that 60% of hyperthyroid patients with atrial fibrillation will revert to sinus rhythm spontaneously when hyperthyroidism is

treated to a euthyroid state⁷.

Three treatment modalities are currently available for the management of hyperthyroidism: antithyroid drugs (ATDs), surgery, and radioactive iodine (RAI) therapy. Treatment for hyperthyroidism is aimed at restoring euthyroidism with ATDs while awaiting disease remission and resolution of autoimmunity or inducing permanent hypothyroidism with subsequent thyroxine replacement by total thyroidectomy or RAI therapy. Beta-blockers (for example propranolol and atenolol) are added to block beta-adrenergic tone for symptomatic relief of palpitations, tachycardia, tremulousness, anxiety, heat intolerance, fatigability and shortness of breath. There is currently no consensus on the “best” treatment option with various practices in different centers and countries. The choice of treatment depends on the cause of hyperthyroidism, patient’s age and preference, severity of disease, glandular size, activity and severity of Graves’ ophthalmopathy, local practices and resources.

ATDs including methimazole, carbimazole, and propylthiouracil are effective treatments that inhibit thyroid hormone synthesis, and have clinically important immunosuppressive effects including reducing serum antithyrotropin receptor antibody concentration with time. Antithyroid drugs are an effective treatment option but these drugs take in most cases between 6 to 8 weeks to achieve euthyroidism. It has also shown to have the highest relapse rate at 52.7% compared to RAI (15%) and surgery (10%) in a recent meta analysis⁸. In addition 13% of patients on ATDs experienced adverse events with rash most common with methimazole and hepatic involvement with propylthiouracil⁸.

Therefore there may be a role for adjunctive treatment added on to ATDs. It may be situations where adjunctive treatment is required to alleviate symptoms and restore euthyroidism rapidly. It may be useful for preoperative preparation or pre radioactive iodine treatment where rapid control is necessary to achieve euthyroidism to prevent the risk of thyrotoxic crisis. It may be helpful to alleviate symptoms of patients with severe hyperthyroidism and especially those who are more vulnerable such as the elderly or patients with heart failure from thyrotoxic cardiomyopathy, and atrial fibrillation. It has been proven useful in thyroid storms. It is also effective in situations where ATDs have failed to control

disease because of ATD resistance, intolerance or poor compliance. There are several adjunctive agents studied previously in literature, namely iodine and iodide containing compounds, lithium, potassium perchlorate, and cholestyramine. We are interested to study the effects of cholestyramine and prednisolone as adjunctive treatment to ATDs in patients with overt hyperthyroidism.

Thyroid hormone is metabolized in the liver where it is conjugated to glucuronides and sulfates and excreted in the bile. Usually only 20% of circulating T₄ is excreted in the bile and released into the intestine and reabsorbed completing the enterohepatic circulation. However in the thyrotoxic states there is an increased enterohepatic circulation of thyroid hormones with an increased urinary and fecal excretion of both conjugated and FT₄⁹. Cholestyramine is an anion exchange resin that binds T₄ in the intestine resulting in fecal excretion of T₄ thus reducing the enterohepatic circulation and absorption in hyperthyroidism. Cholestyramine has been used in cases of thyroid storm¹⁰. Cholestyramine has been studied as an adjunctive therapy to thionamides and found to be effective in reducing thyroid hormones rapidly. Solomon et al first studied the effects of cholestyramine powder (4g QID) on 15 thyrotoxic patients and shown a more rapid decline in all thyroid hormone levels in the cholestyramine group in the first 2 weeks (P<0.01)¹¹. Mercado et al similarly reported rapid decline in total and free T₄ and T₃ when cholestyramine 4g tds was added to methimazole and propranolol¹². Kaykhaei et al. demonstrated a similar efficacy with a lower dose of cholestyramine (2g BD vs 1g BD) with all patients in the cholestyramine group achieving euthyroidism in 4 weeks⁹. The main adverse effects are flatulence and constipation in 10% of cases and vomiting, diarrhea, indigestion, abdominal pain, abnormal stools, bloating, headache, and raised triglyceride levels in 1-10%, whereas muscle pain, raised liver enzymes and difficulty in swallowing are rare¹³. Patients in the trials above tolerated the drug well with only 2 reported hyperdefecation and complained of bad taste¹¹.

Steroids have been shown to be effective in controlling hyperthyroidism. It demonstrates immediate effects by inhibiting the conversion of thyroxine to triiodothyronine peripherally and also blocks the release of thyroxine from the thyroid gland. It may also have the potential to suppress the immune response

and hence decrease stimulation of the thyroid gland in Graves' disease¹⁴. Few case reports have documented its efficacy in situation where rapid control of hyperthyroidism is required. Ozawa in his case series documented that following oral administration of 30 mg daily dose of prednisolone with or without ATDs, both serum T_4 and T_3 concentrations decreased rapidly and reached euthyroidism within 2 weeks and subtotal thyroidectomies were performed uneventfully in all 4 cases¹⁷. Another study reported the addition of betamethasone 0.5mg 6 hourly, iopanoic acid 500 mg 6 hourly and propranolol 40 mg 8 hourly to 14 patients with hyperthyroidism submitted to subtotal thyroidectomy because ATDs have failed to control thyrotoxicosis and found that patients had normal T_3 levels by day 5 and T_4 reduction noted but has not reached normal levels by 5 days of treatment¹⁵. One study reported rapid normalization of thyroid function with prednisolone 20 mg daily as an adjunct when patients develop resistance to maximum treatment of carbimazole¹⁴. There were no reported serious side effects in the case series mentioned above.

Evidence in literature shows that adjunctive therapy such as cholestyramine and prednisolone may have a role to play in the management of hyperthyroidism. So far, studies on cholestyramine have proven its efficacy but they are small in size and have not been recommended in clinical guidelines. There are no clinical trials conducted in the asian population. A Cochrane systematic and current review is currently ongoing by Salazar et al. to assess the efficacy of bile acid sequestrants as a standard adjunctive treatment therapy in hyperthyroidism and whether to recommend it in clinical practice guidelines¹⁸. This study would add weight to the ongoing systematic review. On the other hand, no clinical trials have been conducted to assess prednisolone as an adjunctive therapy to date and the safety profile unknown. We aim to compare the efficacy and safety profile of cholestyramine or prednisolone as adjunctive therapy to no adjunct. We also aim to compare the efficacy of cholestyramine and prednisolone as adjunctive therapy. We hypothesize that with the addition of cholestyramine or prednisolone to ATDs, we are able to achieve euthyroidism more effectively and rapidly compared to ATDs alone which may be useful in many crucial clinical situations described above.

6.1 Potential Risks

Cholestyramine is a bile acid sequestrant that works by increasing the removal of bile acids from the body. The most common adverse reaction is constipation but most instances are mild, transient and controlled with conventional therapy. Other less frequent adverse reactions are abdominal discomfort, flatulence, nausea, vomiting and bleeding tendencies due to hypoprothrombinemia if use long term. Detailed information can be found on the drug leaflet attached at the appendix. Solomon et al. reported all patients tolerated cholestyramine without inordinate difficulty with 2 patients experienced hyperdefecation for a couple of days and all patients complained of the taste of the powders¹¹.

Prednisolone is a corticosteroid and work by modifying the body's immune response to various conditions and decreasing inflammation. In hyperthyroidism it reduces the conversion of T₄ to T₃. The common adverse reactions include fluid retention, alteration in glucose tolerance, elevation in blood pressure, behavioural and mood changes, increased appetite and weight gain. There is a risk of hypothalamic-pituitary-adrenal axis suppression and Cushing's syndrome if given long term. It may increase the risks related to infection but rate of occurrence increases with the dose of steroids. There may be an increase risk of peptic ulcer disease. If used long term may decrease bone density. In a meta analysis, the use of prednisone 35 mg daily for a mean 64 days increased the risk for diabetes (OR 1.7 (1.1-2.6) P= 0.02), hypertension (OR 2.2 (1.4-3.8) P =0.01), dermatologic effects (OR 4.5 (3.5-5.7) P= 0.001) but was not statistically significant association for peptic ulcer, bacterial sepsis, osteoporosis, psychosis and tuberculosis¹⁹. Steroids may cause muscle weakness from renal potassium loss and myopathy if taken long term but there are case reports of thyrotoxic periodic paralysis soon after glucocorticoid administration²². The detailed information regarding risks and adverse reactions to prednisolone can be found in the drug leaflet attached in the appendix.

The immediate risks foreseeable in this study would be the risk of iatrogenic hypothyroidism. However this risk is closely monitored and the event of

iatrogenic hypothyroidism action will be taken. The long-range risks would be the possibility of suppression of the adrenal axis from the prolonged steroid use. However, this risk would be minimised as the prednisolone dose would be tapered over time.

6.2 Potential Benefits

Cholestyramine is a bile acid sequestrant that decreases the enterohepatic circulation of thyroid hormones in subjects with overt hyperthyroidism. Solomon, Kaykhaei, Mercado and Tsai et al. have all demonstrated that Cholestyramine is effective in reducing thyroid hormones with minimal side effects when added to standard therapy for up to 4 weeks of treatment. Although the common side effect is constipation, it may prove useful in hyperthyroid patients with hyperdefecation.

Prednisolone reduces the conversion of T_4 to T_3 in the circulation. Prednisolone 30 mg daily used short term effectively normalised thyroid hormone levels in 2 weeks in a series of 4 cases prior to subtotal thyroidectomy. No adverse reactions reported in this case series. In a similar study using betamethasone 0.5 mg 6 hourly coupled with iopanoic acid (500 mg 6 hourly) and propranolol for 5 days as preparation for hyperthyroid patients for surgery, drug tolerance was excellent with no serious side effects noted even in pregnant patients and no anesthetic incidents or post operative complications.

This study conducted with Cholestyramine or Prednisolone as adjunctive therapy is short term (4 weeks) and therefore minimise long term side effects of both drugs and minimise the risk of iatrogenic hypothyroidism. It has the potential to rapidly reduce thyroid hormones in a short span of time thus achieving euthyroidism promptly, improving thyrotoxic symptoms especially those with severe hyperthyroidism, the elderly and those complicated with fast atrial fibrillation and thyrotoxic cardiomyopathy. It may be useful in preoperative or pre radioactive iodine treatment where there is a need to achieve euthyroidism to prevent risks of thyrotoxic crisis. Prednisolone is readily available in most hospitals in Malaysia and fairly cheap.

This study will provide definitive efficacy and safety information of both

Cholestyramine and Prednisolone as adjunctive treatment in patients with overt hyperthyroidism. The overall benefits of this study outweigh the potential risks.

7 OBJECTIVES

7.1 *Primary objectives:*

1. To assess the efficacy between Cholestyramine plus standard treatment (Carbimazole plus Propanolol), Prednisolone plus standard treatment and standard treatment alone in subjects with overt hyperthyroidism

7.2 *Secondary objective(s):*

1. To assess the safety profile of Cholestyramine plus standard treatment, Prednisolone plus standard treatment and standard treatment alone.

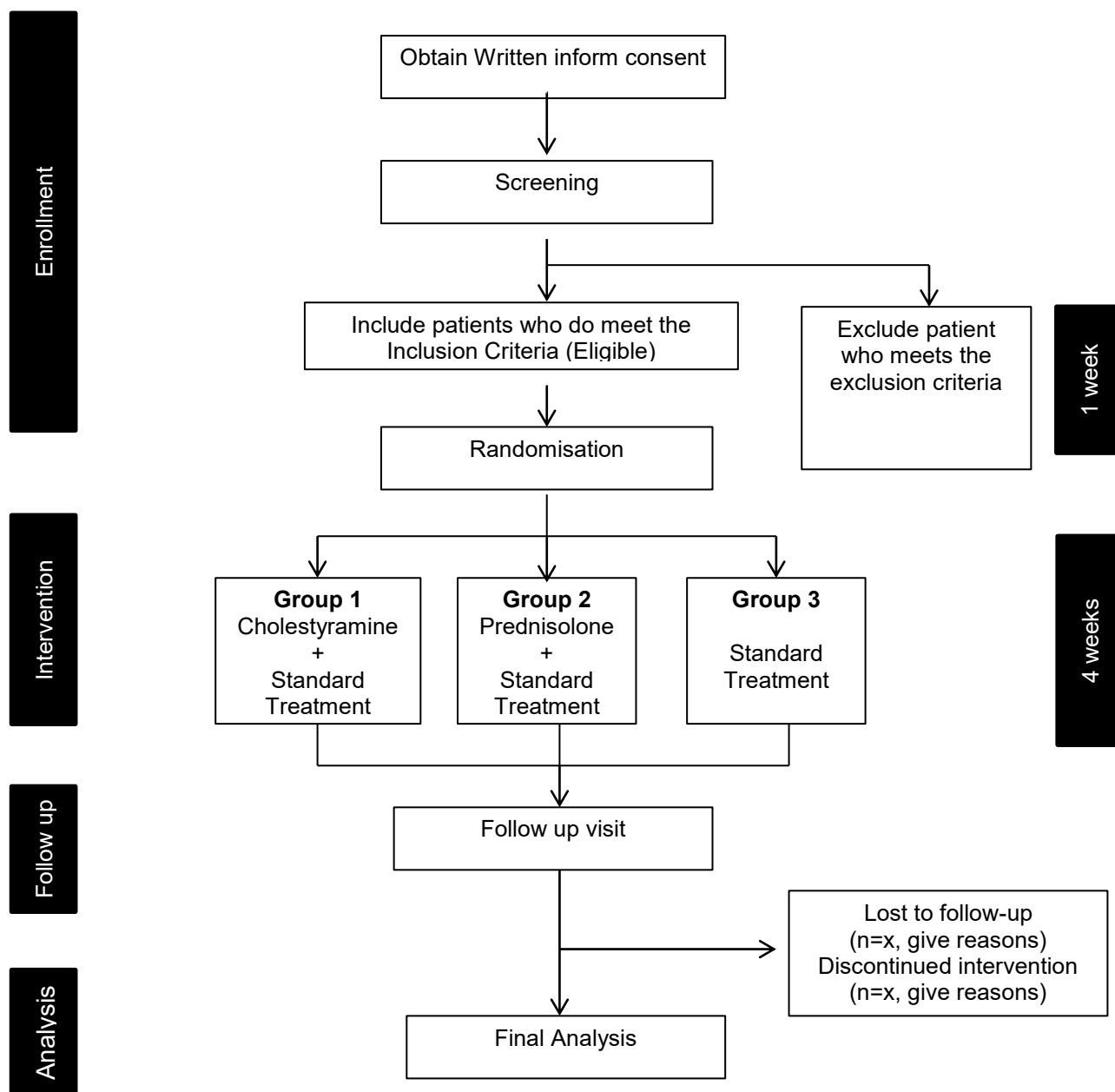
8 STUDY DESIGN

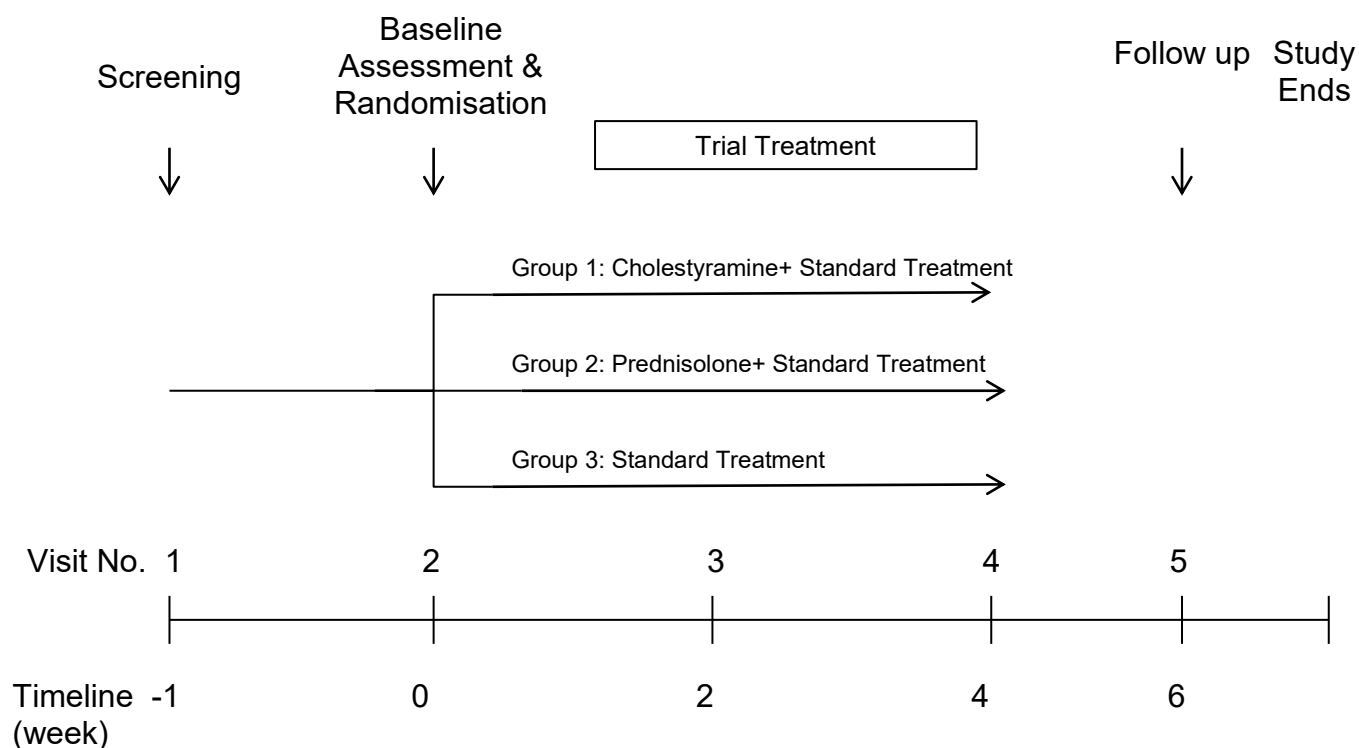
8.1 Overall study design

This a multi-center, open-label, randomised, parallel-group study to compare the efficacy of cholestyramine plus standard treatment versus prednisolone plus standard treatment versus standard treatment alone in the treatment of overt hyperthyroidism. The allocation ratio is 1:1:1.

| Group 1: Cholestyramine plus standard treatment |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cholestyramine powder 4g BD, Tablet Carbimazole 30 mg OD, Tablet Propanolol 40 mg BD for 4 weeks |
| Group 2: Prednisolone plus standard treatment |
| Tablet Prednisolone 30 mg OD for week 1, 20 mg OD for week 2, 10 mg OD for week 3 and 5 mg OD for week 4, Tablet Carbimazole 30 mg OD, Tablet Propanolol 40 mg bd for 4 weeks |
| Group 3: Standard Treatment alone |
| Tablet Carbimazole 30 mg OD, Tablet Propanolol 40 mg BD for 4 weeks |

8.2 Schematic diagram of study design:





8.3 Discussion of study design

All hyperthyroid subjects secondary to Graves disease identified at endocrine, endocrine surgery, general medical clinics and medical wards in Hospital Putrajaya, Hospital Queen Elizabeth II and Hospital Ampang will be screened from May 2017/ Upon approval from MREC to 31st December 2017. Potential participants will be invited to a screening visit.

Screening visit

The screening visit consists of providing information about the study, obtaining informed consent and screening assessment. The investigator will further explain the study, answer any questions and seek informed consent. All subjects will provide written informed consent to their participation in the study. The subject will then have a complete history taking, clinical examination and anthropometric measures. They will have their blood sampled, approximately 10 ml for screening tests. Subjects are eligible for the trial, if they comply with the following inclusion and exclusion criteria.

Baseline visit and Randomisation

Subjects eligible for the trial will return for baseline assessment and randomisation. They will be assigned a unique sequentially numbered study identifier according to the order in which he or she is enrolled in the trial.

The subject will then complete the baseline assessment including history taking, clinical examination, anthropometric measures, blood sampling (6 ml) and imaging (if not done previously). Following baseline assessment, subjects will be randomised into either of the 3 treatment groups. A subject will be randomly allocated to one of the three treatments per random allocation sequence that will be generated by a member of the study team.

Duration

The total trial duration is expected to be 7 weeks (1 weeks screening period, 4 weeks intervention period and 2 weeks follow up period). The intervention period for each subject will be 4 weeks. The subject will return at week 2 and week 4 of intervention for safety and compliance assessment and blood sampling (6 ml each visit) for biochemical monitoring. There will be a follow up visit 2 weeks from the end of intervention period to monitor for any adverse effects and complications and a repeat blood sampling (6ml) for biochemical monitoring.

8.4 Study population

All subjects with current overt hyperthyroidism secondary to Graves' disease who are being referred to or being followed up at Hospital Putrajaya, Hospital Queen Elizabeth II and Hospital Ampang are considered for participation. Patients are eligible for the trial if they comply with the following inclusion and exclusion criteria.

8.4.1 Inclusion criteria

1. Provision of written consent by subject or guardian.
2. Subject of either sex, more than 18 years of age
3. Subjects with moderate to severe overt hyperthyroidism (caused by Graves' disease).
 - Moderate to severe overt hyperthyroidism is defined as Free T₄ > 1.5 times upper limit of normal reference range and TSH below lower limit of reference range, who are either newly diagnosed or previously diagnosed and receiving ATDs currently.
 - Graves disease is defined as hyperthyroidism coupled with clinical signs of symmetrical diffuse goiter, thyroid orbitopathy, or diffuse and vascular thyroid on ultrasound or positive TRAb antibody.
4. Female patients will either be
 - post-menopausal for ≥ 2 years
 - Women of childbearing potential can be included if surgically sterile or using double contraception with at least one method being barrier contraception. Women of childbearing potential must have a negative pregnancy test at screening and at randomisation. Pregnancy tests will be repeated during each visit.

8.4.2 Exclusion criteria

1. Inability or unwillingness to provide written consent.
2. Inability or unwillingness to comply with the requirements of the protocol as determined by the investigator.
3. Pregnancy, breastfeeding or use of non-reliable method of contraception.
4. Subjects with history of chronic liver disease, chronic renal failure, heart failure, diabetes mellitus
5. Subjects with history of peptic ulcer disease, upper gastrointestinal bleeding, diverticulitis or ulcerative colitis.

6. Subjects who have recently had live or attenuated virus vaccines
7. Subjects with current infection (systemic fungal, active tuberculosis, cerebral malaria, viral hepatitis, HIV)
8. Subjects with cataracts and glaucoma
9. Subjects with osteoporosis
10. Subjects with psychiatric disorders
11. Subjects with complete biliary obstruction, bleeding disorders, hypertriglyceridemia (fasting triglyceride levels > 300mg/dL)
12. Previous history of adverse reactions to cholestyramine or other bile acid sequestrants
13. Previous history of adverse reactions to prednisolone or other steroid compound
14. Current use of cholestyramine or prednisolone or other steroid compound
15. Participation in another clinical trial and/or receipt of cholestyramine or prednisolone within 4 weeks prior to screening visit.
16. Subjects with history of bronchial asthma, bronchospasm, peripheral vascular disease or adverse reactions to propranolol
17. Subjects with adverse reactions to carbimazole
18. Hypokalemia (serum K⁺ <3.5 mmol/L)
19. Thyroid storm defined as Burch Wartofsky Score >45

8.4.3 Subject withdrawal & drop-out

Subjects are free to withdraw from the study at any time for any reason. Subjects may also be withdrawn from the study at any time at the discretion of the investigator. The following are anticipated conditions/events that would require a subject to be withdrawn from the study:

- Adverse reactions or intolerance to study drug
- Protocol violation
- Subject requires use of unacceptable concomitant medication

- Subject not compliant with protocol procedures
- Subject develops a condition during the study that violates the inclusion/exclusion criteria
- Lost to follow-up
- Administrative problems
- Death

8.4.4 *Procedures for handling withdrawal*

Subjects who withdraw or are withdrawn from the study should:

- Have the reason(s) for their withdrawal recorded
- Be asked about the presence of any AEs and if so should be followed up by regular scheduled visits, telephone contact, correspondence or home visits until satisfactory clinical resolution of AEs is achieved.
- Be seen by an investigator and all final assessments will be performed and recorded in the OFF STUDY form.
- Be encouraged to continue coming for regular visits and assessments
- Have at least one follow-up contact (scheduled visit, telephone contact, correspondence or home visit) for safety evaluation during the 30 days following the last dose of study treatment.
- In the event of pregnancy, the subject should be monitored until conclusion of the pregnancy and the outcome of pregnancy reported.
- Have study treatment returned.

8.4.5 *Subject replacement policy*

Withdrawn subjects would not be replaced.

8.4.6 *Screening failures*

Patients who fail to meet the inclusion and exclusion criteria are defined as screening failures. A screening log will be maintained which includes screen failures. The log will document the subject number, subject initials, demographics and the reason(s) for excluding the patient from the study. This log will be kept in the Investigator's Study File.

9 TREATMENT AND STUDY PROCEDURES

9.1 Description of study drug

9.1.1 Treatment for Group 1: Cholestyramine group

Cholestyramine 4g twice daily + Carbimazole 30 mg daily+ Propranolol 40 mg twice daily for 4 weeks

Study treatment consists of cholestyramine powder 4g (1 sachet) twice a day and standard treatment which includes tablet carbimazole 30 mg daily and tablet propranolol 40 mg twice a day to be taken orally for 4 weeks.

The trial dosage of cholestyramine is based on available clinical data and is not considered to cause adverse reactions^{9,12}. The trial dosage for carbimazole is based on available clinical data¹⁶ and in line with the current ATA 2016 hyperthyroid guidelines⁴ and our current local standard practice in treating patients with moderate to severe hyperthyroidism. The trial dosage of propranolol is as per ATA 2016 recommendations to provide symptom relief⁴.

Subjects are instructed to mix cholestyramine powder with 60-180 mls of fluid, to be taken before breakfast and dinner and advised to drink plenty of fluids to prevent constipation. It is recommended to take other drugs one hour before or 4-6 hours after cholestyramine to prevent interference from the powders with absorption. Please refer to drug leaflet attached for full description of cholestyramine. Tablet carbimazole is to be taken whole before, during or after meal at the same time of the day. Propranolol should be taken at the same time daily either before or with meals. Please refer to drug leaflet for more information.

9.1.2 Treatment for Group 2: Prednisolone group

Prednisolone 30 mg daily for week 1, 20 mg daily for week 2, 10 mg daily for week 3 and 5 mg daily for week 4+ Carbimazole 30 mg daily+Propanolol twice daily for 4 weeks

The study treatment for Group 2 consists of tablet prednisolone 30 mg daily for week 1, tapered down to 20 mg daily for week 2, 10 mg daily for week 3 and 5 mg daily for week 4 (total 4 weeks) and standard treatment which includes tablet carbimazole 30 mg daily and tablet propanolol 40 mg twice a day for 4 weeks.

There are no previous clinical trials conducted on adding prednisolone as adjunctive treatment for hyperthyroidism. The trial dosage for tablet prednisolone was selected based on a case series by Ozawa et al. as there were no clinical trials, who added 30 mg of prednisolone to patients who were thyrotoxic and intolerant to thionamides. The dose of prednisolone in his case series of 4 patients were either tapered down within a month or maintained at 30 mg daily less than a month. All patients achieved normal thyroid function in 2-4 weeks and underwent subtotal thyroidectomy successfully¹⁷. We have also used similar doses in clinical practice and found it to be effective. Therefore the starting dose for prednisolone in this trial was chosen at 30 mg daily with a tapering down dose over 4 weeks to to minimize potential side effects of prolonged steroid use. Trial dosage for carbimazole and propanolol is as mentioned above

Subjects are instructed to take the tablets in the morning with or after meals to decrease gastrointestinal upset. Subjects are encouraged not to miss any doses and if they do miss a dose, to take it as soon as possible and if it is almost time for the next dose, skip the missed dose and go back to regular dosing schedule and not to take 2 doses at once. They are advised to avoid alcohol while on prednisolone. Please refer to drug leaflet for more information.

9.1.3 Group 3 Standard treatment group

Carbimazole 30 mg daily + Propranolol 40 mg twice daily

Standard treatment group consists of tablet carbimazole 30 mg daily and tablet propranolol 40 mg twice a day for 4 weeks. Please refer to drug leaflet for more information.

9.2 Investigational product supply and handling

9.2.1 Supply, packaging and labeling

Each study drug box will be labeled with the following information:

1. Participant's ID
2. Drug's name
3. Dose
4. Instruction on how to use
5. Storage condition
6. Expiry date
7. PI's name

9.2.2 Storage

The study drug will be stored between 20-25⁰C, protected from moisture and be stored in accordance with the manufacturers' instructions.

The study drug will be kept under adequate security by the investigator and only accessible to authorised study personnel.

9.2.3 Dispensing

Each patient will be dispensed sufficient medication for two weeks of therapy. Upon dispensation, the research pharmacist will write the following in the Investigational Product Dispensing Log: subject ID and initials and date dispensed, the total dose given weekly/monthly and frequency of dosage, total bottles dispensed, batch number and expiry date of product.

9.2.4 *Accountability*

The investigator will maintain current and accurate record of the receipt, inventory and dispensing, including shipping invoices, of all study supplies. The Investigational Product Accountability Log will include:

- Date received
- Delivery order (D.O.#) reference number and amount received and placed in storage
- Name of study medication and dosage
- Amount currently in storage area
- Label ID number or batch number/Lot number
- Amount dispensed to and returned by each subject, including unique subject identifiers

Accountability logs must be available at any time. Upon completion/termination of the study, unused study drug must be returned to the sponsor for reconciliation and destruction.

9.3 Concomitant medication/treatment

A concomitant medication is any medication, other than the trial product, which is taken during the trial. Details of any concomitant medication must be recorded at visit 1. Changes in concomitant medication must be recorded at each subsequent visit as they occur.

Concomitant medications that are not permitted during the study period

Plasma levels and efficacy of prednisolone may be affected by the concomitant use amphotericin B, anticholinesterase agents, CYP 3A4 inducers (e.g. barbiturates, phenytoin, carbamazepine, and rifampin), CYP 3A4 inhibitors (e.g., ketoconazole, macrolide antibiotics), cyclosporine and digitalis. Lithium, Propylthiouracil, Lugols iodine, Contrast medium are not permitted as it will affect the results of the study.

Cautious use of phenylbutazone, warfarin, thiazide diuretics (acidic) as well as tetracycline penicillin G, phenobarbital, thyroid and thyroxine preparations, estrogens and progestins and digitalis as cholestyramine resin may delay or reduce the absorption of these drugs.

9.4 Treatment allocation and randomization

A participant will be randomly allocated to one of the three treatments per random allocation sequence that will be generated by a member of the study team. The allocation ratio is 1:1:1. The random allocation sequence will be generated by using the Web site [Randomization.com](http://www.randomization.com) (<http://www.randomization.com>). Blocked randomisation will be used. The random allocation sequence will be generated by a member of the study team who will not be involved in the enrolment of subjects and assessment of outcomes. The block size of 6 will be used. The allocation sequence generated will be concealed in an opaque sealed envelope with the following information written:

Front page

1. Study title
2. Site name and code

3. Study PI name
4. Protocol number
5. Sequential randomization number

Inside the randomization envelope

1. Study title
2. Site name and code
3. Study PI name
4. Protocol number
5. Sequential randomization number
6. Subject ID
7. Date and time the envelope open
- 8 Signature and name of the person opening the envelope
9. Study treatment the patient is allocated to

The identity of the treatment that will be assigned to each subject will only be revealed on the first day of treatment. Principal Investigator and/or Sub Investigator will screen and enrol the subjects. Principal Investigator and/or Sub Investigator will assign the treatment to each subject, according to the allocation sequence.

9.5 Baseline assessment and laboratory tests

Information on subject's demographics, anthropometric measures and vital signs will be obtained. A detailed history taking of subject's current medical and past medical history along with full clinical examination. Blood sampling will be conducted. Ultrasound thyroid and ECG scheduled and ECHO if needed. UPT will be done prior to randomisation. Please refer to section 12 for more details.

9.6 Assessment of compliance

Adherence will be assessed at each visit during therapy by checking the subject diary card, 2 weekly count of sachets/ tablets from returned bottles. And this will be documented by a member of the study team.

9.7 Discontinuation and interruption of treatment

Participants will be advised to be compliant to study drug at all times and advised to take the missed dose as soon as they can remember and not to take a double dose to make up for missed doses.

9.8 Assessment of efficacy

- Primary efficacy endpoints are:
 1. Proportion of subjects with normal thyroid hormone levels: defined as serum free T₄ or serum Free T₃ levels measured at 2 and 4 weeks after initiation of study treatment.

9.9 Assessment of safety

Safety data will be analysed for the data collected throughout intervention period and up to follow up period. The following endpoints will be collected:

- Number of subjects with adverse effects during the intervention period and follow up period (total duration 6 weeks)
 - Subjects will be asked to report about adverse reactions (specified in the protocol) at 2 weeks, 4 weeks of intervention period and 2 weeks after end of study treatment period.
- Number of subjects with serious adverse events during intervention period and follow up period (total duration 6 weeks)
 - Subjects will be asked to report about SAE immediately during the intervention period and follow up period

Safety and tolerability assessments will consist of:

- Regular performance of physical examinations
 1. BP, PR, Temperature, Weight (kg)
- Regular monitoring of laboratory tests
 2. FPG/ RPG, Electrolytes (Na⁺, K⁺, Urea, Creatinine), FT₄, FT₃, TSH
- Monitoring and recording all adverse reactions and serious adverse events

10 ADVERSE EVENTS

10.1 Definitions

10.1.1 Adverse event (AE)

Any untoward medical occurrence in a subject administered an investigational product and which does not necessarily have a causal relationship with treatment.

An AE includes:

1. A clinically significant worsening of a concomitant illness
2. A clinical laboratory adverse event: a clinical laboratory abnormality which is clinically significant, i.e an abnormality that suggests a disease and/or organ toxicity and is of a severity that requires active management, Active management includes active treatment or further investigations, for example change of medicine dose or more frequent follow-up due to the abnormality.

The following should be reported as AE:

Treatment of emergent symptoms which include:

- Medical conditions or signs or symptoms that was absent before starting study treatment.
- In this trial the following events must be collected and reported:
 1. SAEs
 2. AEs leading to discontinuation of study drug
 3. Gastrointestinal symptoms
 - a. Constipation
 - b. Bloating
 - c. Diarrhea
 - d. Abdominal pain
 - e. Vomiting
 4. Diabetes
 5. Hypokalemia
 6. Hypothyroid

- The following abnormal laboratory values particularly to this study will be observed
 - Fasting plasma glucose more ≥ 7 mmol/L or Random plasma glucose ≥ 11.1 mmol/L
 - Serum K⁺ < 3.5 mmol/L
 - TSH above upper limit of reference range and FT₄ normal or below lower limit of reference range
- Any doubtful event should be treated as an AE.

10.1.2 *Unexpected adverse event*

Any adverse event not reported in the safety section of the Investigator's Brochure or if the event is of greater frequency, specificity or severity.

10.1.3 *Serious adverse event (SAE)*

Any adverse event occurring that:

- Results in death
- Is a life threatening adverse experience defined as any adverse event that places the subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred. Note that this does not include a reaction that had it occurred in a more severe form, it would have caused death.
- Results in subject hospitalisation or prolongation of existing hospitalisation.
- Subject becomes pregnant while on study drug

The following hospitalisations are not considered to be SAEs:

- Those planned before entry into the study
- Elective treatment for a condition unrelated to study indication or study treatment
- Occur on an emergency outpatient basis and do not result in admission (unless fulfilling other criteria in SAE definition)
- Part of normal treatment or monitoring of the study indication and are

not associated with any deterioration in condition.

- Results in a significant or persistent disability or incapacity defined as any event that results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions.
- Is any instance of overdose, either accidental or intentional (suspected or confirmed)
- Is any other important medical event, based upon appropriate medical judgement, that may jeopardise the subject or may require medical or surgical intervention to prevent or avert one of the outcomes listed above.

10.2 *Detecting and documenting AE*

Information about all AEs, whether volunteered by the patient, discovered by investigator questioning or detected through physical examination, laboratory test or other means, would be documented on the Adverse Event Form and followed up as appropriate. The AE form should be faxed to the coordinating investigator Dr. Serena Khoo Sert Kim at fax number 03-88889169 and email sk_liv@rocketmail.com.

When eliciting experiences of AE from a subject, ask a standard non-leading question like "Do you feel different in any way since starting the new treatment/the last visit?" This question will be put to the subject in his/her own language at each study visit.

Each AE should be described by:

1. Nature of AE

This should be documented in terms of a medical diagnosis(es). When this is not possible, the AE should be documented in terms of signs and/or symptoms observed by the investigator or reported by the subject.

2. Duration

Start and end dates

3. Assessment of causality

The investigator should attempt to explain each AE and assess its

relationship, if any, to the study treatment. Causality should be assessed using the following definitions:

- Very likely
 - The AE follows a reasonable temporal sequence from study treatment administration
 - Abates upon discontinuation of study treatment
 - Reappears on repeated exposure (re-challenge)
- Probable
 - The AE follows a reasonable temporal sequence from study treatment administration
 - Abates upon discontinuation of study treatment
 - Cannot reasonably be explained by known characteristics of the subject's clinical state
- Possible
 - The AE follows a reasonable temporal sequence from study treatment administration
 - But could have been produced by the subject's clinical state or other mode of therapy administered to the subject
- Doubtful
 - The temporal association between study treatment and AE is such that the study treatment is not likely to have any reasonable association with the observed event
- Very unlikely
 - The AE is definitely produced by the subject's clinical state or other mode of therapy administered to the subject

The degree of certainty with which an AE is attributed to study treatment or alternative cause like natural history of disease or concomitant treatment should be guided by the following considerations:

- Time relationship between treatment and occurrence of AE
- De-challenge and re-challenge information, if applicable
- Known pharmacology of the drug
- Dose response relationships
- Lack of alternative explanations i.e. no concomitant drug used and no other inter-current disease

- Reaction of similar nature being previously observed with this drug or class of drug
- Reaction having often been reported in literature for similar drug

4. Severity of AE

- Mild: awareness of signs or symptoms, but they are easily tolerated
- Moderate: enough discomfort to cause interference with usual activity
- Severe: incapacitating, with inability to work or do usual activity.

Note that a severe AE is not necessarily serious. The term severe is a measure of the intensity while a serious AE is determined based on regulatory criteria. A life threatening AE is an SAE.

5. Final outcome

- Recovered/ resolved- The subject has fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity after the subject signed the informed consent
- Recovering/resolving- The condition is improving and the subject is expected to recover from the event. This term is only applicable if the subject has completed the trial or has died from another AE.
- Recovered/ resolved with sequelae- The subject has recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as SAE.
- Not recovered/not resolved- The condition of the subject has not improved and the symptoms are unchanged, or the outcome is not known.
- Fatal- This term is only applicable if the subject died from a condition related to the reported AE.
- Unknown- This term is only applicable if the subject is lost to follow-up

10.3 Reporting SAE

Information about all SAE will be documented in the AE form and reported to Coordinating Investigator of the study – Dr. Serena Khoo Sert KIm (Fax

number: 03-88889169, email: sk_liv@rocketmail.com) and MREC directly within 24 hours.

10.4 Treatment and follow up of AE

Treatment of any AE is at the sole discretion of the investigator who should follow up subjects with AE until the event has resolved or until the condition has stabilised. Otherwise appropriate medical care should be arranged for the patient. Abnormal tests should be repeated until they return to baseline levels or an adequate explanation of the abnormality has been found.

1. Treatment of over-dosage significant enough to cause adverse effects

- Study medication must be stopped immediately and subject be monitored closely for all adverse reactions. Immediate thyroid function test to be sent and reviewed.

2. Pregnancy

- A female subject must be instructed to stop taking study medication and immediately inform the investigator if she becomes pregnant during the study. The investigator should counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the foetus. Monitoring of the subject should continue until conclusion of the pregnancy. The investigator should report all pregnancies to the coordinating investigator and MREC within 24 hours of being notified of the pregnancy.
- Pregnancy occurring in the partner of a subject participating in the study should also be reported to the investigator and sponsor. The partner should be counseled and followed as described above. Pregnancies will be formally reported as SAEs.

3. Hypokalemia

- If mild hypokalemia (3-3.5 mmol/L), to replace with Mist Potassium Chloride and reassess K⁺ levels after 3 days. If moderate to severe hypokalemia (<3 mmol/L), to assess for symptoms and consider admission for close monitoring, ECG and oral/IV potassium replacement. To consider withdrawing treatment (especially prednisolone) if refractory to active intervention.

4. Diabetes

- To reconfirm by sending a repeat FPG and 2 hour post prandial glucose. Upon confirming diagnosis of diabetes, consider starting oral hypoglycemic drugs. Consider discontinuing study treatment if severe uncontrolled hyperglycemia or hospitalisation for hyperglycemic emergencies.

5. Hypothyroid

- Hypothyroid is defined as symptoms of hypothyroidism coupled with elevated TSH more 4.7mU/L and normal or low levels of Free T4 <9 pmol/L measured during intervention with study drug
- If hypothyroidism occurs during study treatment, stop study treatment and repeat thyroid function test one week later. Thyroid function tests will be reviewed and medication adjusted. All adjustment to medications will be documented in CRF. No thyroxine will be given as hypothyroid will recover upon discontinuing study treatment. Subject will discontinue study treatment if develop persistent and severe profound symptoms of hypothyroidism

6. Hyperthyroid and thyroid storm

- If subjects are still hyperthyroid (no reduction in Free T4 and Free T4 from baseline) at the end of week 4, Carbimazole will be increased in accordance to the standard practice. In the event if subjects are symptomatic of thyrotoxicosis throughout trial period, propranolol doses may be increased as per clinician judgement and documented in CRF. In the event that subject develops thyroid storm during trial period, SAE will be reported, study treatment discontinued and treatment of thyroid storm with lugol's iodine, beta blockers, hydrocortisone and high doses of propylthiouracil will be initiated as per standard practice.

10.5 Safety update

Any safety updates will be notified to MREC

11 STUDY CONDUCT

11.1 *Study visits and procedures*

11.1.1 *Screening visit (Week -1, Visit 1)*

1. Screening of all overt hyperthyroid subjects due to Graves disease
2. Assess subject for eligibility to enter study according to the inclusion and exclusion criteria.
3. Obtain written consent from subject or parent/guardian.
4. Obtain medical history
 - a. Hyperthyroid history
 - b. Past medical history
 - c. Cardiovascular complications of hyperthyroidism
 - d. Family history of thyroid disease
 - e. Smoking history
 - f. Medication history
5. Perform baseline measurements of vital signs (BP, HR, Temperature) and anthropometric measurements (Height (cm), Weight (kg) and BMI)
6. Perform complete examination including
 - a. Presence of Graves Ophthalmopathy and disease activity
 - b. Thyroid examination
 - c. Cardiovascular examination including presence of atrial fibrillation
7. The following screening tests are done (Total of 10 mls of blood will be sampled). All screening blood tests will be sent to **respective site's own laboratory** for analysis.
 - a. Free T₄, Free T₃, TSH
 - b. Hep Bs Ag, Anti HCV ab, HIV1/2 ab
 - c. FBS/RBS
 - d. FLP
 - e. Liver function test
 - f. Renal function test

- g. FBC
 - h. UPT (For all women of childbearing age)
8. Record all screened subjects in the Screening Log regardless of whether or not the subject has been enrolled in the study.
 9. Refer to the study activities table below.

11.1.2 Baseline visit (Week 0, Visit 2)

1. Subjects who are eligible for the study after reviewing both inclusion and exclusion criteria will be called up for a baseline visit no longer than **1 weeks** from screening visit.
2. Perform baseline measurements of vital signs (BP, HR, Temperature) and anthropometric measurements (Height (cm), Weight (kg) and BMI
3. Perform complete medical history and physical examination if not done during screening visit
4. Record any concomitant medications
5. The following baseline tests will be performed (Total of 6 mls of blood will be sampled). **Thyroid function test and TRAb levels will be sent to central lab (Gribbles laboratory)** whereas the other tests will be conducted at respective site.
 - a. Free T₄, Free T₃, TSH
 - b. TRAb levels
 - c. UPT (For all women of childbearing age)
 - d. ECG
 - e. ECHO if evidence of thyrotoxic cardiomyopathy
6. Complete relevant section/page of the CRF.
7. Subject who has fulfilled all inclusion and exclusion criteria and has completed baseline assessment will proceed to randomisation into any of the 3 treatment groups on the **same day**.
8. Refer to the study activities table below

11.1.3 *Randomisation*

A participant will be randomly allocated to one of the three treatments per random allocation sequence that will be generated by a member of the study team not involved in the subject enrolment and concealed in an envelope.

11.1.4 *Study treatment and visits*

Study treatment (Visit 3 Week 2)

The investigator will perform the following procedures:

1. Medical history taking
2. Record any concomitant medication
3. Record any change of dose administration of study treatment and assess compliance
4. Record any AE or SAE
5. Perform physical examination including vital signs (BP, HR, Temperature, Weight)
6. Obtain blood sample (total of 6 mls of blood will be sampled). Thyroid function test will be sent to central lab (Gribbles laboratory) whereas the others will be sent to respective site's laboratory. (FT₄, FT₃, TSH, FBS/RBS, Blood urea and serum electrolytes)
7. UPT for women of childbearing age
8. Complete relevant section/page of CRF
9. Dispense study treatment
10. Refer to the study activities table below

Study treatment (Visit 4 week 4)

The investigator will perform the following procedures:

1. Medical history taking

2. Record any concomitant medication
3. Record any change of dose administration of study treatment and assess compliance
4. Record any AE or SAE
5. Perform physical examination including vital signs (BP, HR, Temperature, Weight)
6. Obtain blood sample (total of 6mls of blood will be sampled). Thyroid function test will be sent to central lab (Gribbles laboratory) whereas the others will be sent to respective site's laboratory. (FT₄, FT₃, TSH, FBS/ RBS, Blood urea and serum electrolytes)
7. UPT for women of childbearing age
8. ECG
9. Complete relevant section/page of CRF
10. Dispense study treatment
11. Refer to the study activities table below

11.1.5 Follow up visit (Visit 5, Week 6)

Safety assessment to monitor for adverse events, monitor for symptoms and signs of adrenal insufficiency and monitor for iatrogenic hypothyroidism.

1. Medical history taking
2. Perform physical examination including vital signs
3. Record any AE or SAE
4. Obtain blood sample (total of 6 ml of blood will be sampled). Thyroid function test will be sent to central lab (Gribbles laboratory) whereas the others will be sent to respective site's laboratory. (FT₄, FT₃, TSH, Blood urea and serum electrolytes/ FBS or RBS)

Study Activities Table

| | Screening | Baseline Assessment and Randomisation | Treatment | | Follow up |
|-----------------------------------------|-----------|---------------------------------------|-----------------|-----------------|-----------------|
| Visit | 1 | 2 | 3 | 4 | 5 |
| Timeline (wks) | -1 | 0 | 2 | 4 | 6 |
| Procedures | | | | | |
| Informed consent | X | | | | |
| Check eligibility | X | | | | |
| Blood sample for screening ^a | X | | | | |
| Randomisation | | X | | | |
| Patient demographics | X | | | | |
| Medical History | X | | | | |
| Complete physical exam | X | | | | |
| Height (cm), Weight (kg) | X | X | X | X | X |
| Vital signs (BP, HR, Weight, Temp) | X | X | X | X | X |
| FT ₄ & FT ₃ & TSH | X | X (central lab) | X (central lab) | X (central lab) | X (central lab) |
| TRAb levels | | X (central lab) | | | |
| FBS/ RBS | X | | X | X | X |
| BUSE | X | | X | X | X |
| UPT ^b | X | X | X | X | |
| U/S Thyroid | | X | | | |
| ECG | | X | | X | |
| ECHO ^c | | X | | | |
| Efficacy assessment | | | X | X | |
| Concomitant medication | | | X | X | |
| Report AE and SAE | | | X | X | X |
| Dispense study treatment | | | X | X | |
| Assess compliance | | | X | X | |
| Complete relevant section of CRF | | | X | X | X |

^a HepBsAg, Anti HCV ab, HIV1/2 ab, FBC, BUSE/Creatinine, LFT, FBS/RBS, FLP. Written consent will be taken for HIV test. All blood tests on screening visit including thyroid function test will be sent to the respective site's laboratory.

^b For women of childbearing age

^c Only if clinically suggestive of thyrotoxic cardiomyopathy or has atrial fibrillation

11.2 *Criteria for stopping subject treatment*

The investigator will discontinue a subject's taking of study treatment at any time if the subject:

1. Who no longer wishes to participate in the trial and wishes to withdraw from the study at any time
2. Experiences intolerable adverse reactions
3. Is diagnosed with any of the exclusion criteria during the intervention period
4. Develops hypothyroid during the intervention period (Hypothyroid is defined as symptoms of hypothyroidism coupled with elevated TSH > 4.7 mU/L and normal or low levels of Free T4 <9 pmol/L)

In all these cases, the investigator and/or the treating physician will if possible encourage the subject to continue with the follow up assessment and to allow the use of collected data in the analyses.

11.3 *Sample handling and analysis*

11.3.1 Collection

The only biospecimen involved in this study is blood. Blood draws of 5-10 mls would be performed as stated in the study activities table and before the dose of study drug. Blood specimen will be taken by a dedicated nurse or doctor.

The blood tests for **screening visit** will be sent to the **respective site's own laboratory**. The tests are:

- Free T₃, Free T₄, TSH
- HepBsAg, Anti HCV ab, HIV1/2 ab
- Full Blood Count
- Renal function test

- Liver function test
- Fasting blood sugar/ Random blood sugar (FBS/RBS)
- Fasting lipid profile

Subsequent FBS/RBS, renal profile for study treatment visits and follow up visits will also be sent to the respective site laboratory. Screening thyroid function tests results will not be analysed and therefore would not require specimens to be sent to a central laboratory.

Free T₄, Free T₃, TSH and TRAb levels for baseline and randomisation visit, study treatment visits (Visit 3 Week 2 and Visit 4 Week 4) and follow up visit (Visit 5 Week 6) will be sent to the centralised laboratory (Gribbles Pathology Laboratory Central Headquarters) for processing.

Request form with the patient's particulars shall be duly filled at the hospital site. Specimen should be individually packed in a specimen carrier bag with the request form. A call should be made by Site coordinator to Gribbles Pathology Careline number (1300-88-0234) for specimen pick up. Gribbles courier will be dispatched for specimen collection. Specimen transport will be done using a cooler bag (cool transport). Specimens will be collected by courier from the hospital site.

After checking the specimen from the courier, the laboratory staff will proceed to process the sample. Specimens are centrifuged prior to sending it for analysis. Once centrifugation is done, the blood specimen is sent to the central headquarters laboratory for analysis. After test has been done, results are reviewed and if needed, validated before release.

Pre and post counselling test would be offered for HIV test in line with general practice and if positive be notified as per Malaysian law. Specimens would not be stored for future research.

11.3.2 Labeling

- The specimens will be labeled the study protocol number, subject number, subject initials, study day and name of test.

11.4 Laboratory analysis

| # | Test | Method |
|---|---------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1 | Free T ₄ | <ol style="list-style-type: none"> 1. Type of kit : SIEMENS HEALTHCARE DIAGNOSTIC (SIEMENS HEALTHINEERS) 2. Name of analyser : CENTAUR Xp 3. Type of sample: Serum (recommended) 4. Methodology: Direct Chemiluminescence competitive immunoassay 5. Measuring range : 1.3 - 155 pmol/L 6. Imprecision (CVs) : This assay exhibits total imprecision of $\leq 7.3\%$ CV 7. Reference ranges : Adult : 9-25 pmol/L |
| 2 | Free T ₃ | <ol style="list-style-type: none"> 1. Type of kit : SIEMENS HEALTHCARE DIAGNOSTIC (SIEMENS HEALTHINEERS) 2. Name of analyser : CENTAUR Xp 3. Type of sample : Serum (recommended) 4. Methodology : Direct Chemiluminescence competitive immunoassay 5. Measuring range : FT3 : 0.3 - 30.8 pmol/L 6. Imprecision (CVs) : This assay exhibits total imprecision of $\leq 3.7\%$ 7. Reference ranges : Adult : 3-6.5 pmol/L |

| | | |
|---|-------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 3 | TSH | <ol style="list-style-type: none"> 1. Type of kit : Siemens Healthcare Diagnostic (Siemens Healthineers) 2. Name of analyser : Centaur Xp 3. Type of sample : Serum (recommended) 4. Methodology : TSH: 3RD Generation Antibody capture. 5. Measuring range : 0.008 - 150 μIU/L 6. Imprecision (CVs) : This assay exhibits total imprecision of $\leq 3.8\%$ 7. Reference ranges : Adult : 0.4-4.7 mU/L |
| 4 | TRAb levels | <ol style="list-style-type: none"> 1. Type of kit : Euroimmun Anti TSH Receptor (TRAb) ELISA (IgG) 2. Name of analyser : EUROANALYSER 3. Type of sample : Serum only 4. Methodology : ELISA 5. Measuring range : 0.16 to 40 IU/ml 6. Imprecision (CVs): Interassay variation (n=20) with mean of 18.57 IU/ml is CV of 7.6% 7. Reference ranges : Negative: <1.0 IU/ml Positive: >1.0 IU/ml 8. Storing and packaging of sampling instructions and methods: Serum sample storage 2-8°C for up to 14 days |

12 DATA MANAGEMENT

Data will be written and collected from the CRF. Data collected will be transferred to an Excel sheet. Accurate and reliable data collection will be assured by verification and cross-check of 100% of the CRFs against the investigator's records (source document verification). The investigators will have access to the data and will be stored until the study period ends. The clinical data (hardcopy) will be archived and stored for 7 years. It will be destroyed after 7 years. The softcopy of the medical records of the subjects will remain in Electronic Medical Records (EMR) which will depend on the hospital's record office Protocol of Storage. The responsibility of the data handling and storage lies with the investigators and the sponsor.

13 STATISTICAL METHODS

13.1 Sample size and power considerations

The sample sizes estimations and analyses plan were made with the caveat that the three-treatment groups comparison is as little difference from carrying out a series of three independent trials, and to use conventional significance tests without adjustment as argued by Saville (1990)²⁰. Sample size and power considerations

Sample sizes were estimated by using PASS 11 software²¹. The estimations were based on primary objectives only.

Primary objective: To achieve 80% power to detect a 30% difference in the proportions achieving normal **FT₄** between Group 3 (Carbimazole+Propanolol) and each of Group 1 (Cholestyramine + Carbimazole+ Propanolol) and Group 2 (Prednisolone+ Carbimazole+ Propanolol), 41 patients are needed in each group. The proportion achieving normal FT₄ in Group 3 was estimated to be 40%. (1) Allowing for 10% drop out rate, the sample size required is therefore 45 per arm. The test statistic used is the two-sided Z test with pooled variance.

The significance level was targeted at 0.05.

Primary objective: To achieve 80% power to detect a 30% difference in the proportions achieving normal **FT₃** between Group 3 (Carbimazole+Propanolol) and each of Group 1 (Cholestyramine + Carbimazole+ Propanolol) and Group 2 (Prednisolone+ Carbimazole+ Propanolol), 41 patients are needed in each group. The proportion achieving euthyroid status in Group 3 was estimated to be 40%. (1) Allowing for 10% drop out rate, the sample size required is therefore 45 per arm. The test statistic used is the two-sided Z test with pooled variance. The significance level was targeted at 0.05.

Thus, the final sample size will be 45 per group.

13.2 Analysis

Data entry, cleaning and analyses will be done using SPSS version 21. Categorical data will be described by using proportions and numerical data will be described by using mean, median, standard deviation, and/or interquartile range, as appropriate. The analyses will be based on the intention-to-treat

13.2.1 Baseline Comparability

Baseline characteristics will be compared between the 3 groups using the appropriate descriptive statistics. No formal hypothesis test will be made for baseline comparison.

13.2.2 Efficacy Analysis

1. For the primary objectives, all comparisons of means between treatment will be analysed using one-way ANOVA and all pairwise comparisons of proportions will be analysed by using two-sided Z test and 95% confidence interval of the estimated difference will be calculated. Alpha level will be set at 0.05 and no

adjustment will be made for the multiple pairwise comparisons. Analysis will be based on intention to treat and per protocol analysis.

2. For secondary objectives, all comparisons of means between treatment will be analysed using one-way ANOVA and all comparison of proportions will be analysed using chi-square test of independence.

Alpha level will be set at 0.05. Analyses will be based on safety set analysis.

14 ADMINISTRATIVE MATTERS

14.1 Notification of regulatory authority(ies)

All necessary arrangements for the registration and approval of this study with the responsible authorities and the disposition of the required data and document will be undertaken by the Principal Investigator.

14.2 Notification of primary care physician

The General practitioner or primary care physician will be informed of the subject's involvement in this study. This is so that if the patients need to see their own physician for any reason, the physician will be aware that they are taking a study drug.

14.3 Study initiation

The study will begin only after getting the approval from MREC.

14.4 Protocol deviation

Any protocol deviation will be documented by the Investigator with rectification as soon as possible. The investigator should be notified immediately. With the exception of emergency situations, no changes or deviations in the conduct of this protocol will be permitted without the prior approval from MREC. In the event of any emergency, the investigators will institute any medical procedures deemed appropriate. All such procedures must be promptly reported to MREC.

14.5 Study documentation

All documentation will be maintained. These documents are Essential Documents and Source Documents.

14.5.1 Essential documents

These are documents that permit evaluation of the study and the quality of the data produced. The Essential Documents are:

- Signed protocol amendments
- Sample CRFs
- MREC approval letter
- Informed consent form
- CV of investigator and co-investigator
- Investigational product accountability and shipping records
- Other appropriate documents in accordance with GCP guidelines.

The investigator will maintain an Investigators Study File. This file shall be used to facilitate and ensure filing of all relevant and Essential Documents during and after the study. The investigator will be responsible for keeping the Investigator's Study File updated and ensuring that all required documents are filed. The file will be inspected during monitoring visits.

14.5.2 Source documents

These are original hospital records, clinical charts, subject screening checklist, original laboratory reports, pharmacy dispensing records, and records kept at the pharmacy, at the laboratories and at medico-legal departments involved in the study. All source documents would be kept confidential of personal information.

The investigator must maintain source documents for each patient in the study. All information on CRFs must be traceable to these source documents:

- Patient identification list
- Curriculum vitae

14.6 *Patient identification list/Enrolment log*

An enrolment log will be maintained that contain a list of all enrolled patients containing the full name, date of birth, date of enrolment, and the randomization number. The list has to show an unequivocal study identification number. The list will be filed in the Investigator's Study File on site.

14.7 *Curriculum vitae*

The investigator will provide curriculum vitae showing his/her experience in the area of the proposed study. These should be filed at CRC as well as in the Investigator's Study File on site.

14.8 *Retention of documents*

All study documents will be or at least 3 years after completion or discontinuation of the study.

If the investigator moves or retires, he/she must nominate someone in writing to be responsible for archiving. Archived data may be held in microfiche or electronic record, provided a back up exists and a hard copy can be obtained from it if required.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made with CRC to store these in a sealed container(s) outside of the site so that they can be returned sealed to the investigator in case of a regulator audit. Where source documents are required for the continued care of the subject, appropriate copies should be made for storage outside of the site.

14.9 *Finance*

The study will be funded by the Ministry of Health Malaysia to support the work of the investigator and supply the required investigational product for the study.

14.10 *Study Termination and Site Closure*

The study may be terminated early if there is:

- Deliberate violation of the signed protocol
- The incidence and/or severity of adverse events in this or other studies indicate a potential health hazard caused by the treatments under trial.

14.11 *Confidentially*

The investigator agrees that all information will be kept strictly confidential.

14.12 *Publication policy*

The investigator shall have the right to publish or permit the publication of any information or material relating to or arising out of the work. Publishing will protect the confidentiality of subjects' personal information.

14.13 *Anticipated subject accrual and duration of the study*

This study is expected to start in April 2017. The projected study timetable for the study is as follows:

- First patient enrolled is expected in March/ April 2017
- Last patient enrolled is expected in December 2017
- The last patient enrolled is projected to complete the treatment period in December 2017

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16 APPENDICES

- Declaration of Helsinki
- Study Procedures
- Questionnaire and CRF (*if applicable*)
- Investigational product labels
- Elements of informed consent
- Sample informed consent form (in different languages)
- Patient information sheet (in different languages)
- Letter of indemnity
- Investigators' curriculum vitae

