RECORMON (ERYTHROPOIETIN) AND VENOFER (IRON SUCROSE) COMPARED TO BIOSIMILAR PRODUCTS IN MANAGEMENT OF RENAL ANAEMIA IN ADULTS

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To my late dad, Sakaya Musavini Nambwa. 8th April 2014.

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ABBREVIATIONS AND ACRONYMS

CGN	Chronic glomerulonephritis
CKD	Chronic Kidney Disease
DM	Diabetes Mellitus
EPO	Erythropoietin
ESA	Erythropoiesis stimulating agents
ESRD	End stage renal disease
FSGN	Focal segmental /sclerosing glomerulonephritis
Hb	Hemoglobin
HD	Hemodialysis
HHD	Hypertensive heart disease
HTN	Hypertension
IV	Intra venous
KNH	Kenyatta National Hospital
MTC	Medicines and Therapeutics Committee
PET	Pre-eclamptic toxemia
RBCs	Red blood cells
RPGN	Rapidly progressive glomerulonephritis
TBC	Total Blood Count

OPERATIONAL DEFINITION OF TERMS

Biopharmaceuticals

Are pharmaceutical products that are biological in nature and manufactured using biotechnology involving use of live organisms, typically done using cell cultures.

Biosimilars

A biosimilar is a biological product that is highly similar to the reference product not withstanding minor differences in clinically inactive components, and lacking clinically meaningful differences between it and the reference biologic product in terms of the safety, purity and potency.

Generic

A pharmaceutical product intended to be interchangeable with the innovator product in an individual patient usually manufactured without a license from the innovator company and marketed after expiry of patent or other exclusivity rights.

Bioequivalence

Is defined as "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study".

Recormon-Recormon arm

Study arm in which patients were on Recormon and Venofer throughout the study period, they were not switched in August 2014.

Recormon-Relipoietin arm

Study arm in which patients were switched from Recormon and Venofer to Relipoietin and Ferrose in August 2014.

ABSTRACT

Background

The kidneys are complex organs, and they are vital in maintaining normal body functions. The kidney has two main functions: blood filtration and production of hormones. These hormones help regulate blood pressure (renin), make red blood cells (erythropoietin) and regulate blood calcium levels (Calcitriol). In chronic kidney failure there is reduced production of the hormone erythropoietin which leads to renal anemia. This refers to the reduction in hemoglobin levels due to an absolute reduction of the total number of circulating red blood cells (RBCs arising from chronic renal disease. Current use of recombinant human erythropoietin to ameliorate anemia in patients with chronic renal disease has been very successful and has shown that the primary cause of the anemia found in almost all patients with renal failure is due to a deficiency in the production of erythropoietin. In the month of August 2014 there was a change in products used in management of renal anemia at KNH from erythropoietin beta (Recormon) and Venofer to the biosimilar EPO alpha (Relipoietin) and Ferrose. No study on comparison of treatment outcomes as a result of this change has been conducted.

Objective

To compare the effectiveness of multisource erythropoietin and iron sucrose injections with the branded products in adult patients being treated for renal anemia at Kenyatta National Hospital.

Methodology

This was a descriptive longitudinal hospital-based, retrospective before-after study with two arms, making use of sampled medical records of 140 renal anemia patients at Kenyatta National Hospital renal department. The first arm had 73 patients who were on the original product (Recormon) since August 2012 while the second arm had 67 patients who were on the original product until August 2014 when they were switched to the generic brand (Relipoietin). Ethical approval was granted by Kenyatta National Hospital/University of Nairobi Ethics and Research Committee – P29/01/2015. Files were retrieved and sampled universally for data extraction and data was recorded on a pre-tested data collection form. Descriptive and inferential data analysis was done using Statistical Package for the Social Sciences (SPSS) version 20.

Results

Of the 140 patients enrolled in the study 94 (67.6%) were male. The mean age was 50.46 years (±15.49 [SD]), and 98 (70%) of the patients had been diagnosed with CKD. The most commonly encountered comorbidities were hypertension 87 (33.3%), Diabetes mellitus 80 (30.7%) and concurrent hypertension and diabetes 26 (10.0%). Seventy seven (58.6%) of the sampled population had their hemoglobin increase and, of these, 43(63.2%) were from the Recormon-Recormon (Original brand) arm. There was a marginal but non-significant decrease in the mean hemoglobin levels for those patients who were switched from Recormon to Relipoietin (mean difference = 0.011; 95%CI: -0.26, 0.28). The independent predictors of increased hemoglobin levels were being atenolol-free [OR 6.4 (1.3-32.2)] p value=0.02 and having a diagnosis of CKD [OR 2.3 (1.0-5.2)] p value=0.04.

Conclusion

The patients did not have significantly different mean hemoglobin levels while on Recormon than when switched to Relipoietin. However, it is recommended that clinicians regularly monitor hemoglobin levels when they switch from a reference to a biosimilar erythropoietin product. Health care providers need to be educated on the differences between original and biosimilar erythropoietin to ensure they understand difference in potency or effectiveness and monitor the hemoglobin levels.

CHAPTER 1: INTRODUCTION

1.1 Background

Anemia refers to an absolute reduction of the total number of circulating red blood cell (RBCs). Renal anemia is deficiency of erythropoietin production that is caused by failure of the kidneys to produce the hormone. Prevalence of renal anemia is estimated to be 8–16% worldwide. In Kenya there exists no statistics on the burden of renal anemia. However in Kenyatta National Hospital (KNH) the burden of renal disease in the months of January and October 2014 was 1656 in- patients out of which mortality was 694. Core management of renal anemia includes the use of Recombinant human erythropoietin which has been shown to be effective and can eliminate the need for blood transfusions.

Biosimilars are biotechnological products that are proved to be comparable to an already approved reference product in quality, non-clinical and clinical evaluation. Healthcare professionals need to understand the critical issues surrounding the use of biosimilars to make informed treatment decisions. Verification of the similarity of biosimilars to innovator biopharmaceuticals remains a key challenge. This study will compare effectiveness of Recormon plus Venofer (original products) and Relipoietin plus Ferrose (biosimilar products) through treatment outcomes.

1.2 Functions of the kidneys

The kidneys are complex organs, and they are vital in maintaining normal body functions. They have two main functions; blood filtration and production of hormones that help regulate blood pressure (Renin), synthesize red blood cells (Erythropoietin) and regulating blood calcium levels (Calcitriol) [1]

Calcitriol is the active form of vitamin D in the body and increases the absorption of calcium from food in the intestinal lumen. Renin is a proteolytic enzyme secreted by the kidney in response to fall in blood pressure. Erythropoietin (EPO) is a hormone produced by cells of the peritubular capillaries in response to hypoxia (a low level of oxygen in the blood). EPO stimulates the cells of bone marrow to increase their output of red blood cells [2].

1.3 Renal anemia

Anemia refers to an absolute reduction of the total number of circulating red blood cell (RBCs). Anemia is present when the hemoglobin concentration in blood is decreased: in adults and children above 15 years Hb is less than 13.0 g/dl in males and 12.0 g/dl in females, in children 6months to 5 years Hb less than 11.0 g/dl, 5-12 years less than 11.5 g/dl, 12-15 years less than 12.0 g/dl [2]. Etiologically anemia is categorized into 3 groups, decreased RBC production, increased RBC destruction, and blood loss. Anemia of chronic kidney disease (CKD) is categorized under decreased RBC production while based on the morphology of the RBCs; it is classified as normochromic normocytic anemia.

In Kenya there exists no statistics on the burden of renal anemia. However in Kenyatta National Hospital (KNH) the burden of renal disease in the months of January and October 2014 was 1656 in- patients out of which mortality rate was 694 (42 %) [3]**.** The economic and health related quality of life (HRQL) burden of non-dialysis CKD-related anemia is substantial. Under-treatment of renal anemia may contribute to higher resource consumption and higher costs [4]. The Health and Nutrition Examination Survey (NHANES III) states that the burden of renal anemia defined as Hb less than 11g/dl was 800,000 adults in the United States [5].

The burden of anemia in hemodialysis patients is substantial, leading to considerable morbidity, mortality and reduced quality of life. Lower hemoglobin concentrations were associated with higher morbidity and mortality in European hemodialysis patients [8].

1.4 Management of renal anemia

Much progress has been made in recent years in the management of anemia associated with chronic renal failure to using recombinant human erythropoietin (r-Hu EPO) [1]. Current use of recombinant human erythropoietin (r-Hu EPO) to ameliorate the anemia in patients with chronic renal disease has been spectacularly successful and has shown that the primary cause of the anemia found in almost all patients with renal failure is due to a deficiency in the production of EPO [10]. To ensure that full benefit from erythropoietin therapy is received, most patients require iron supplement during treatment. Iron deficiency results in an inadequate response to r-Hu EPO and is the main cause of resistance to this treatment [11, 12].

1.5 Biosimilars

1.5.1 Biosimilars and Bioequivalence

Biosimilars are biotechnological products that are proved to be comparable to an already approved reference product in quality, non-clinical and clinical evaluation. They are considered generics substitutes of original biologics (biopharmaceuticals).

Bioequivalence refers to the absence of significant difference in the availability of active ingredient at the site of action. Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent and their bioavailability (rate and extent of availability) after administration in the same molar dose are similar to such a degree that their effects, with respect to both efficacy and safety, can be expected to be essentially the same.

1.5.2 Biosimilar products for management of renal anemia

A number of products from different manufacturers and countries of origin are available for management of renal anemia. Table 1 shows the products that are registered for use in renal management in Kenya by the Pharmacy and Poisons Board [3].

Table 1-Biosimilar products for management of renal anemia

Originator product	Biosimilars
Recormon injection	Relipoietin 2000 and 4000 iu
500-30000 iu	Eritrogen 2000 and 4000 iu
	Erykine 2000 and 4000 iu
	Epotin 2000 and 4000 iu
	Eprex
	Vintor
	Wepox
Venofer injection	Ferrose sucrose

There was a change in products used in management of renal anemia at KNH from erythropoietin beta (Recormon) and Venofer to the biosimilar EPO alpha (Relipoietin) and Ferrose, and this study sought to examine the clinical implications of this changes by assessing hemoglobin levels in patients that were subjected to this change.

CHAPTER 2: LITERATURE REVIEW

2.1 Anatomy and functions of the Kidneys

2.1.1 Location

Kidneys are a pair of organs found along the posterior muscular wall of the abdominal cavity. The left kidney is located slightly more superior than the right kidney due to the larger size of the liver on the right side of the body. Unlike the other abdominal organs, the kidneys lie behind the peritoneum that lines the abdominal cavity and are thus considered to be retroperitoneal organs. The ribs and muscles of the back protect the kidneys from external damage. Adipose tissue known as perirenal fat surrounds the kidneys and acts as protective padding [2].

2.1.2 Structure

Kidneys are bean-shaped with the convex side of each organ located laterally and the concave side medial. The renal capsule provides a stiff outer shell to maintain the shape of the soft inner tissues. The renal pelvis exits the kidney at the renal hilus, where urine drains into the ureter [2]. The renal arteries branch directly from the abdominal aorta and enter the kidneys through the renal hilus. The renal vein exits the kidney and joins with the inferior vena cava, which carries blood back to the heart [2]. Each kidney contains approximately a million nephrons, the kidneys' microscopic functional units that filter blood to produce urine. The nephron is made of 2 main parts: the renal corpuscle and the renal tubule. A series of tubes called the renal tubule concentrate urine and recover non-waste solutes from the urine. The renal tubule carries urine from the glomerular capsule to the renal pelvis [2].

2.1.3 Physiology of the Kidneys

The main hormonal functions of the kidneys are regulating blood pressure, calcium metabolism, and red blood cell production [14]. It is significant in the excretion of waste products resulting from protein metabolism and muscle contraction and maintenance of a constant fluid environment in the body (Homeostasis). The kidney functions can be lost to a great extent (>90%) without experiencing any symptoms [15].

The kidneys filter blood as it passes through the capillaries that form the glomerulus. Filtrate next passes through the ascending limb of the loop of Henle as it exits the medulla. The urine exits the collecting duct and joins with urine from other collecting ducts in the renal pelvis. Kidneys are able to control the volume of water in the body by changing the reabsorption of water by the tubules of the nephron [2]. The kidneys regulate the pH level of the blood by controlling the excretion of hydrogen ions (H^+) and bicarbonate ions (HCO_3^-). The tubule cells may also actively secrete additional hydrogen ions into the urine when the blood becomes extremely acidic. Sodium (Na^+), potassium (K^+), calcium (Ca^{2+}) and magnesium (Mg^{2+}) are vital electrolyte for muscle function, neuron function, blood pressure regulation, and blood volume regulation. Most of the reabsorption of the ions takes place in the proximal convoluted tubule and ascending loop of Henle. The proximal convoluted tubule and ascending loop of Henle reabsorb about 90% of the chloride ions filtered by the kidneys [2].

2.2 Renal anemia

Under normal physiological conditions, hypoxia in the kidney leads to an increase in the production of erythropoietin, which subsequently stimulates erythropoiesis. When kidneys start to fail, little or no EPO is produced and this results in a failure of red cell production. Another factor causing anemia in kidney disease can be iron deficiency as iron is not absorbed so well when kidneys start to fail, this therefore causes renal anemia. Anemia has been associated with more severe adverse outcomes, such as cardiovascular complications including left ventricular hypertrophy and congestive heart failure [2].

Table 2-Summary table of the various etiologies, classifications and types of anemia [16–18]

	Type	Classification
Etiologies	Blood loss	Acute , Chronic
	Hypoproliferative (impaired production)	Iron deficiency
		Megaloblastic- nuclear cytoplasmic asynchrony,VitB_{12} or folic acid deficiency
		Anemia of chronic disease
		Myelophthisic (infiltrative)
		Aplastic anemia
	Hemolytic (Increased destruction)	Extrinsic to RBCs- auto immune, physical or chemical agents
		Intrinsic to RBCs - membrane defects, metabolic, hemoglobinopathies, chain synthesis defects, amino acids substitution
Morphology	Normocytic normochromic (RBC size and Hb content normal, reduced numbers of RBCs)	Acute blood loss, anemia of chronic disease
		Hemolytic anemia
		Aplastic anemia due to bone marrow failure
	Microcytic hypochromic anemia (RBCs smaller than nucleus of a normal lymphocyte with increased central pallor)	Heme synthesis defect
		Fe deficiency anemia and anemia of chronic disease
		Thalassemias (genetic decrease in beta or alpha globin chain synthesis needed for Hg A). Sideroblastic anemia, Lead poisoning,
	Macrocytic normochromic anemia	Megaloblastic anemia secondary to deficiency or abnormal metabolism of vitamin B_{12} and folate
		Non Megaloblastic anemia
		Liver disease, alcoholism, post splenectomy, neonatal macrocytosis, stress erythropoiesis.

2.2.1 Pathogenesis of renal anemia

Pathogenesis of renal anemia includes chronic inflammation, iron deficiency and shortened half-life of erythrocytes. Normocytic normochromic anemia regularly develops in renal failure when the glomerular filtration rate drops below 20-30 ml/min. This is due to moderately reduced red cell life span, blood loss and an inadequate increase in erythropoiesis relative to the fall in hemoglobin (Hb). The life-span of red blood cells may be shortened by their reduced resistance to mechanical, osmotic or oxidative stress, as well as by extra corpuscular factors. Blood loss occurs due to dialysis, diagnostic sampling and in particular, occult gastrointestinal bleeding [19].

The predominant cause of inadequate erythropoiesis is a failure to increase EPO production in response to the developing anemia. Serum EPO levels in patients with chronic kidney disease are usually within the normal range and thus fail to show an appropriate increase with decreasing hemoglobin levels, as found in non-renal anemia. Both alterations in the function of EPO-producing cells and perturbations of the oxygen-sensing mechanism in the kidney may contribute [20]. Accumulation of a number of toxic metabolic end products may also play a role in the pathogenesis of the anemia [10].

2.2.2 Epidemiology of chronic kidney disease and renal anemia

In the study conducted by Jha V. *et al* the prevalence of chronic kidney disease in the world was estimated to be 8–16% [21]. In 2007, the adjusted annual incidence rate for patients aged 45–64 was 611 per million population. The rate for those aged 75 and older rose by 10.4 percent during the same period to 1,735 and that for patients age 20–44 grew by 5.5 percent to 126 per million population [22].

Anemia is common among those with diabetes and CKD and greatly contributes to patient outcomes [23]. One of the complications of diabetes mellitus is diabetic nephropathy, a progressive kidney disease caused by angiopathy of capillaries in the kidney glomerulus. It is characterized by nephrotic syndrome, which refers to kidney disease with proteinuria, hypoalbuminemia and edema. Nephrotic-range proteinuria is 3 grams per day or more. On a single spot urine collection, it is 2 g of protein per gram of urine creatinine [24].

It is estimate that one in five patients with diabetes and stage 3 CKD have anemia, and its severity worsens with more advanced stages of CKD [25]. CKD leads to end stage renal disease (ESRD).

Diabetes mellitus (DM) affects 9.4 million people in Africa. The prevalence of diabetic nephropathy is estimated to be 6-16% in sub Saharan Africa [26], making diabetes mellitus an important determinant of renal disease and therefore renal anemia in Africa. Kenya with a population of 38.6 million is estimated to have a prevalence of ESRD of 15.6 per million population [27]. In Kenya, a study done in 2009 showed the prevalence of DM to be at 4.2% [28].

The prevalence of CKD is much higher in Asia & Australia than in USA and Europe and is highest in Africa. It continues to increase in USA where in 1990 – 2000; prevalence increased by 30% [29]. The national kidney foundation and kidney disease outcomes qualitative initiative (NKF-KDOQI) indicates that the total prevalence of CKD in USA and Europe was 13% in the year 2004.

Table 3-Prevalence of CKD in USA and Europe according to kidney failure stages [29]

NKF-KDOQI Stage	USA	EUROPE
Stage 1	6.3%	5.7%
Stage 2 & 3	5.5%	4.6%
Stage 4	0.6%	0.7%
Stage 5	0.6%	0.7%

2.2.3 Etiology

In patients with chronic kidney disease, normochromic normocytic anemia mainly develops from decreased renal synthesis of erythropoietin. The anemia becomes more severe as the glomerular filtration rate (GFR) progressively decreases. No reticulocyte response occurs, red blood cell survival is decreased and there is an associated increased bleeding tendency due to uremia-induced platelet dysfunction [20]. Iron deficiency is also common in patients with CKD.

The deficiency may be absolute iron deficiency, often due to poor dietary intake or sometimes occult bleeding or functional iron deficiency, when there is an imbalance between the iron requirements of the erythroid marrow and the actual iron supply.

Iron deficiency leads to a reduction in formation of red cell hemoglobin, causing hypochromic microcytic anemia. Other causes for anemia in chronic kidney disease include the presence of uremic inhibitors e.g. parathyroid hormone, inflammatory cytokines, reduced half-life of circulating blood cells and deficiencies of folate or vitamin B_{12} [30].

2.2.4 Prognosis

Patients with chronic kidney disease (CKD) generally experience progressive loss of kidney function and are at risk of end-stage renal disease (ESRD). The rate of progression depends on age, the underlying diagnosis, the success of implementation of secondary preventive measures, and the individual patient. Possible mechanisms include renal ischemia caused by reduced oxygen delivery due to low Hb and underlying heart failure. Anemia may worsen renal medullary hypoxia, leading to renal interstitial injury and fibrosis [31]. Timely initiation of chronic renal replacement therapy is imperative to prevent the uremic complications of CKD that can lead to significant morbidity and death [32].

Gouva *et al* (2004) conducted a randomized controlled trial of early versus deferred initiation of erythropoietin in non-diabetic predialysis patients where early treatment was initiated on 45 patients and deferred treatment for 43 patients and followed for 22.5 months. The study concluded that early initiation of erythropoietin in predialysis patients with non-severe anemia significantly slows the progression of renal disease and delays the initiation of renal replacement therapy [33].

2.2.5 Manifestation of chronic renal failure caused by anemia

Patients with anemia of chronic disease may present with the following symptoms: Generalized weakness or malaise, easy fatigability, generalized body aches/myalgia. Orthostatic symptoms e.g. lightheadedness, dizziness, syncope or near-syncope, decreased exercise tolerance, chest discomfort, palpitations, cold intolerance, sleep disturbances, inability to concentrate, loss of appetite**.** The following physical findings may be noted as shown in Table 4 [31].

Table 4-Signs and symptoms of anemia of chronic renal failure

Body system	**Signs and symptoms**
Skin	Pallor
Neurovascular	Decreased cognitive ability, impaired concentration and cognition
Eyes	Pale conjunctivae
Cardiovascular	Orthostatic hypotension, tachyarrhythmia's
Pulmonary	Tachypnea
Abdomen	Ascites, hepatosplenomegaly, anorexia,
Others	bleeding tendency, malaise, depression and lethargy, reduced exercise tolerance, endocrine abnormalities, musculoskeletal symptoms, impaired libido/impotence

2.2.6 Complications of renal anemia

Cardiovascular diseases are a leading cause of death in end-stage renal disease largely as a result of the progressively increasing age of patients and the broad constellation of uremia-associated factors that can adversely affect cardiac function [32]**.**

Symptoms include uremic cardiomyopathy where patient has expansion of extracellular volume and high blood flow. Anemia the potential cause of cardiac volume overload, ischemic heart disease that occurs due to changes in cardiac muscle function and structure which is caused by reduction in perfusion and low oxygen supply. There is also irregular heartbeat or an unusually fast heartbeat, especially when exercising, harmful enlargement of muscles in the heart and heart failure which is a long-lasting condition where the heart can't pump enough blood to meet the body's needs.

Neurological complications whether due to the uremic state or its treatment contribute also to the morbidity and mortality in patients with renal failure. Despite continuous therapeutic advances, many neurological complications of uremia, like uremic encephalopathy, atherosclerosis, neuropathy and myopathy fail to fully respond to dialysis [34].

2.3 Management of renal anemia

The European Best Practice Guidelines (EBPG) for the Management of anemia in Patients with Chronic Renal Failure were developed by a working group made up of representatives of the European Renal Association/European Dialysis and Transplantation Association (ERA-EDTA) and the national nephrology societies of a cross-section of European countries. EBPGs cover the following topics: diagnosis of the anemia of chronic renal failure, indications for starting treatment with epoietin, recommended minimum target hemoglobin concentrations, epoietin dosage and route of administration, assessing and optimizing iron stores, causes and management of epoietin resistance, and possible adverse effects of epoietin treatment [35].

Kidney Disease Improving Global Outcomes (KDIGO) is a global independent volunteer-led self-managed charity incorporated in Belgium. Its mission is to improve the care and outcomes of kidney disease patients worldwide through the development and implementation of global clinical practice guidelines [36]. Guidelines are designed to provide information and assist decision making. They are intended to define a standard of care and should not be construed as one, nor should they be interpreted as prescribing an exclusive course of management. According to Issue 4 volume 2 Clinical Practice Guideline for Anemia in Chronic Kidney Disease, the following summary of recommendation statements on CKD are provided [3].

Use of iron to treat anemia in CKD

Balance the potential benefits of avoiding or minimizing blood transfusions, ESA therapy, and anemia-related symptoms against the risks of harm in individual patients when prescribing iron therapy.

Guide subsequent iron administration in CKD patients based on Hb responses to recent iron therapy, as well as ongoing blood losses, iron status tests (TSAT and ferritin), Hb concentration, ESA responsiveness and ESA dose in ESA treated patients, trends in each parameter and the patient's clinical status. Evaluate and test iron status (TSAT and ferritin) more frequently when initiating or increasing ESA dose, when there is blood loss, when monitoring response after a course of IV iron and in other circumstances where iron stores may become depleted.

When the initial dose of IV iron dextran or non-dextran is administered patients should be monitored for 60 minutes after the infusion. Avoid administering IV iron to patients with active systemic infections [3].

Use of ESAs and other agents to treat anemia in CKD

In initiating and maintaining ESA therapy, balance the potential benefits of reducing blood transfusions and anemia-related symptoms against the risks of harm in individual patients (e.g. stroke, vascular access loss and hypertension). ESAs are generally not used to maintain Hb concentration above 11.5 g/dl (115 g/l) in adult patients with CKD. Choice of an ESA should be based on the balance of pharmacodynamics, safety information, clinical outcome data, costs and availability. True biosimilar products should be used [3].

Red cell transfusion to treat anemia in CKD

To minimize the general risks related to red cell transfusions, use should be avoided as much as possible when managing clinical anemia. In certain acute clinical situations, patients are transfused when benefits of red cell transfusions outweigh the risks; these include, when rapid correction of anemia is required to stabilize the patient's condition (e.g. acute hemorrhage, unstable coronary artery disease) or when rapid pre-operative Hb correction is required [3].

Dialysis patients were the frequent recipients of blood transfusions approximately every 2-3 weeks. This, however, subjected patients to complications such as blood-borne viruses, iron overload and increased sensitivity to major histocompatibility antigens lessening the chances for successful kidney transplantation.

There are two main products that are used currently to manage renal anemia. The main aim is to raise hemoglobin level to above 11g/dl with hematocrit of 33-36%**.** These are:

Recombinant human erythropoietin alpha or beta

Human erythropoietin is a sialglycoprotein composed of 165 amino acids. Human erythropoietin was purified in 1977 and the human erythropoietin gene was isolated by Lin in 1985. Recombinant human erythropoietin (rHuEPO) therapy was introduced in 1986-7[44–46].

A study was done in Europe to determine efficacy of erythropoietin (Recormon) on patients with chronic kidney failure where 32 patients ranging from 18-77years were treated with Recormon from baseline to week 5 and Hb level measured. The mean rise in Hb level was from 7.7 to 11g/dl which concluded that Recormon corrected the anemia and eliminated the need for transfusion in these patients [37,38].

Optimal dosing interval for erythropoietin injection remains unknown. This led to a systematic review that included 33 studies to determine the optimal frequency of ESA administration in terms of efficiency and effectiveness. Four interventions were compared using different frequencies: 2 weekly interval, 4 weekly, 2-3 weeks interval, once/week, once per month or 2-3 times per week. Continuous Erythropoietin Receptor Activators (CERA) vs. other ESAs, Darbopoetin using different frequencies, Darbopoetin vs. rHuEPO and rHuEPO using different frequencies.

It was shown that long-acting ESAs (Darbopoetin and CERA) administration at 1-4 weeks interval are non-inferior to 1-3 times/week rHuEPO in achieving Hb target without any significant difference in adverse events in hemodialysis patients [39].

Another study was done to show the cost-efficacy of subcutaneous route of epoietin beta and the conclusion was that sub-cutaneous epoietin beta is an alternative treatment and a cost effective option for anemia management as it combines a well-established safety and efficacy record as compared to the alpha moiety, tolerability and a convenient once weekly dosing with potential to reduce treatment cost by up to 30% [40].

Iron sucrose or Iron gluconate

Iron sucrose, also known as iron saccharate, is a complex of polynuclear iron (III)-hydroxide in sucrose for intravenous use. Iron sucrose has a molecular weight of approximately 34,000 – 60,000 Daltons. The number of sucrose molecules bound to iron varies during the manufacturing process [41]. These drugs are effective and eliminate the need for transfusion which has higher risks of immunological sensitizations, infections and iron overload and restores hematocrit to normal levels in patients with renal anemia [42].

A number of observational studies have shown an association between degree of anemia in CKD and an increased risk of death. Foley *et al* (1996) prospectively followed 432 ESRD patients and found that each 1 g/dl increase in hemoglobin was associated with a 14% decrease in mortality risk [43]. Most of the studies done on the two brand products (Recormon and Venofer) separately were mainly focused on efficacy of the drug to that of different salt of similar drug, dosage schedule/frequency of administration either once weekly, twice weekly, safety of the drug or tolerability, route of administration either I.V or S.C and bioequivalence.

In an RCT done on efficacy and safety of iron sucrose and iron gluconate, high dose Venofer (iron sucrose) 250mg/month was equally effective in maintaining Hb (efficacy) and equally well tolerated (safety) as low dose of ferrlecit (iron gluconate) at a dose of 62.5mg once/week [44].

In a study where use of Venofer for iron deficiency correction in patients undergoing programmed dialysis was compared to use of oral iron showed that Venofer is both clinically and cost effective compared to oral preparations. It was shown that target Hb was achieved 2.5 times more for those on I.V Venofer as compared to when they were on oral iron preparations [45].

In a study, 162 patients were randomized and one group received ferumoxytol (feraheme) an iron replacement injection and the second group was given Venofer injection. Efficacy and safety was then compared.

Overall adverse events was 48% for patients on ferumoxytol while those on Venofer had 65%, related adverse events was 10% as opposed to 16% in patients on Venofer, adverse events leading to discontinuation was 1% compared to 5% in patients on Venofer and serious adverse events was 9% in patients using ferumoxytol compared to 7% for those on Venofer. Overall increase in Hb was similar in both groups and therefore concluded that the drugs showed comparable efficacy and adverse events (safety) [46].

Clinical practice guidelines recommend intravenous iron because oral supplements are ineffective in correcting iron deficiency.

Serious adverse events have occurred with a single injection of iron leading to a multicentre study done in the U.S. Iron status was defined according to K/DOQI guidelines and for patient that were iron deficient then iron replacement was done while those that were iron replete then a maintenance dose was given. Venofer injection was used in this study and the conclusion was that iron was safe for both replacement and maintenance because none of the participants had life threatening drug related adverse events [47].

In the U.S, 2 *in vitro* studies were designed to study the dializability of iron sucrose and dextran from simulated body system. *In vitro* hemodialysis system was designed to be used for the study and it was shown that both irons dialysate concentrations were below the lower limits assay (<2ppm). The study concluded that both irons are not dialyzable by high efficiency or high flux dialysis membrane regardless of ultra-filtration rate over 4 hour hemodialysis session [35].

Another study looked at the incidence of developing pulmonary infection in hemodialysis patients receiving I.V iron and patients were randomized into 3 different groups. The three groups were administered with i.v iron as shown in Table 5 below;

Table 5-Summary of patients groups receiving i.v iron in different dose and duration

GROUP	DOSE/WEEK	TOTAL DOSE	DURATION (DAYS)
1	3	10	28
2	3	20	70
3	1	10	70

It was shown that the risk of developing infection was dose dependent rather than length/duration of treatment because group 2 patients reported higher incidence of pulmonary infections [48].

Studies on treatment with EPO in CKD patients including diabetics have demonstrated a beneficial effect on kidney disease progression.

Kuriyama *et al* studied 108 patients with stage 3–4 CKD with or without anemia. Those with anemia were randomized to ESA treatment or no treatment. The time to a doubling of serum creatinine from baseline was the study's primary end point. They found that anemia, per se, is a factor in the progression of end-stage renal failure and that reversal of anemia by EPO can retard the progression of renal failure, especially in nondiabetic patients, provided that blood pressure control, rate of increase in hematocrit and dietary protein restriction are appropriate [49].

Gouva *et al*. (2004) Randomized 88 anemic stages 3–5 CKD patients to early versus late treatment with erythropoietin-α to test the hypothesis that this intervention would slow the rate of progression to end-stage renal disease (ESRD). They found that early initiation of erythropoietin in predialysis patients with non-severe anemia significantly slows the progression of renal disease and delays the initiation of renal replacement therapy [40].

Rossert *et al*. (2006) performed a randomized controlled trial involving patients with stage 3–4 CKD and anemia to test the hypothesis that treatment of anemia with an ESA to reach a higher Hb level would slow decline in kidney function. Subjects were targeted to one of two Hb levels (13–15 or 11–12 g/dl) and followed for 12 months. Though the study was terminated prematurely due to labeling changes in Eprex, results showed that the decline in GFR was numerically less in the high-Hb group with improvement in quality of life and vitality [50]

2.4 Management of renal anemia in KNH

There are no local guidelines for management of renal diseases in Kenya.

KNH uses an internal formulary (KNH formulary 2013) to manage anemia associated with chronic renal failure. Recombinant human EPO is given as IV injection initially at 40 units/kg three times a week for 4 weeks and increased according to response to 80 units/kg three times weekly. If needed, a further increase at intervals of 4 weeks in steps of 20 units/kg is recommended. For maintenance, dose is initially reduced by half then adjusted according to response at intervals of 1-2 weeks to a maximum of 720 units/kg per week. Injectable Iron is given according to body weight and iron deficit.

The products administered are dependent mainly on availability in the pharmacy. Until August 2014, Recormon and Venofer were the products available in KNH pharmacy. There has since been a change of the products to Relipoietin and Ferrose respectively.

2.5 Problem Statement

Renal anemia is the leading cause of morbidity and mortality in chronic kidney disease [8]. Additionally there is accompanying significant loss of productivity due to hospitalizations, costs of treatment and strain on the healthcare system. In KNH between January and October 2014 the number of patients admitted with renal disease and complications of renal anemia were 1656, 694 deaths occurred.

The core management plan of renal anemia is using erythropoietin stimulating agents (ESA) and iron injection. Various product types are available in the renal anemia market space, varying in brands and active pharmaceutical ingredient (API) attributes such as alpha or beta erythropoietin.

In the month of August 2014 there was a change in products used in management of renal anemia at KNH from erythropoietin beta (Recormon) and Venofer to the biosimilar EPO alpha (Relipoietin) and Ferrose following what had been procured in the hospital pharmacy. Recormon and Venofer being originator brands are unaffordable to most KNH patients. No study justification on comparison of treatment outcomes as a result of this change has been conducted. This study sought to compare treatment outcomes by monitoring hemoglobin levels in patients that were subject to this change in the study period.

2.6 Study Justification

Healthcare professionals need to understand the critical issues surrounding the use of biosimilars to make informed treatment decisions. Verification of the similarity of biosimilars to innovator biopharmaceuticals remains a key challenge [59]. There is consistent change in the products used in management of renal anemia among branded original and biosimilars.

Bioequivalence studies are not always carried out in resource strained settings, and no such studies have been carried out in Kenya. This study compared effectiveness of Recormon plus Venofer and Relipoietin plus Ferrose through treatment outcomes. It aimed to provide useful information to policy makers and therapeutic committees in making decisions on changes of therapeutic interventions for renal anemia. Changes are based on cost-benefit analysis (Pharmaco-economics) and due to availability of numerous biosimilars to choose from.

2.7 Objectives

2.7.1 Main objective

To compare the effectiveness of multisource erythropoietin and iron sucrose injections with the branded products in adult patients being treated for renal anemia at Kenyatta National Hospital.

2.7.2 Specific objectives

1. To compare the effects of replacement of Recormon and Venofer injections with Relipoietin and Ferrose sucrose injections on the levels of hemoglobin in patients with anemia due to renal insufficiency.
2. To evaluate the need for blood transfusion, hospital admissions and mortality rate among adult patients diagnosed with renal anemia and managed with erythropoietin and iron sucrose injection.
3. To determine the influence of demographics, clinical characteristics and missed doses on changes in hemoglobin in patients with anemia due to renal insufficiency.

2.7.3 Hypothesis

1. The rate of change in the levels of hemoglobin in patients treated with originator brand of erythropoietin is greater than rate of change in patients treated with a biosimilar product.

2. Patients managed with original brand are able to maintain normal hemoglobin of at least 11g/dl for longer duration.

3. Anemia episodes, number of hospitalizations and mortality rates were lower when patients were using the original brands as compared to when they were on biosimilar products.

2.8 Expected outputs of the study

The study will provide information on change in hemoglobin levels in renal anemia patients treated using either Recormon plus Venofer or Relipoietin plus Ferrose injections and also compare other outcomes such as mortality, need for blood transfusions and hospital admissions.

Economically, the information will be useful to medicines and therapeutics committees (MTCs) in deciding on procurement preferences based on efficacy and cost effectiveness.

For policy makers and the ministry, the information will be useful in developing treatment guidelines for managing patients with renal anemia.

Clinically, this information will also useful to the regulators and policy makers in making regulatory decisions especially on the need for full local bioequivalence studies as pre marketing authorization requirements.

Main measure of disease burden will be rate of mortality of renal anemia patients on the biosimilar products and this is crucial because it will help in prioritizing actions in health, assessing performance of healthcare systems, identifying high-risk populations and setting priorities in health research

CHAPTER 3: METHODOLOGY

3.1 Study design

The study was a descriptive longitudinal study carried out from 21st April-30th June 2015. It was a hospital-based, retrospective before-after study, making use of the medical records of renal anemia patients. Hemoglobin levels, number of hospital admissions and mortality related to complications of renal failure of the patients when they were on Recormon plus Venofer was compared to after they were put on Relipoietin plus Ferrose.

3.2 Study site

This study was carried out at the records department of Renal Unit of Kenyatta National Hospital (KNH). KNH is the largest teaching and referral hospital in East Africa. The KNH renal unit is both an in-patient and outpatient clinic that serves as both a primary care Centre and a public referral Centre for renal patients from all over Kenya. Currently the department admits approximately 165 renal disease patients per month [5].

3.3 Study population

The study involved a review of medical records of adult patients with anemia due to renal insufficiency at Renal Unit in KNH who were started on Relipoietin and Ferrose from August 2014 and were on Recormon and Venofer from August 2012 to July 2014.

3.3.1 Inclusion Criteria

Adult patients of age 18-70 years who had been on erythropoietin therapy for anemia due to renal insufficiency for at least two years before August 2014 and have complete records for this period.

3.3.2 Exclusion Criteria

The study excluded any patient with incomplete records or had not used the branded products for more than two years.

3.4 Sample size determination and sampling technique

The study being longitudinal, Twisk sample size calculation was used because more than one follow-up measurement was carried out and the purpose of the study was to compare the development in the outcome variable along the total follow-up period. The outcome variable being continuous, the following equation was applied [60].

$$N = \frac{[Z\ (1-\alpha/2) + Z\ (1-\beta)\ ]^2\ \sigma^2(\ r+1)\ [1+\ (T-1)\ \rho]}{v^2\ r\ T}$$

Where:

N = sample size

$Z_{(1-\alpha/2)}$ = (1- α/2) percentile point of the standard normal distribution -where α = 0.1 (1.96)

$Z_{(1-\beta)}$ = (1- β) percentile point of the standard normal distribution -where β = 0.2 (1.28)

σ = standard deviation of the outcome variable (1.2)

r = ratio of the number of subjects in the compared groups (1:1 which is equivalent to 1)

T = number of follow-up measurements (4)

ρ = correlation coefficient of the repeated measurements (0.5)

v = is the difference in mean value of the outcome variable between the groups (0.25)

Therefore:

$$\mathrm{N} = \frac{[1.96 + 1.28]^2\ \ 1.2^2\ (1+1)\ [1+(4-1)\ 0.5]}{0.25^2\ \mathrm{x}\ 1\ \mathrm{x}\ 4}$$

N = 71

71 were taken to be sample size for one arm. The study had two arms thus total sample size for the study was 142.

The arm on Recormon-Recormon (never switched medication) had 73 files reviewed while second arm who had switched from Recormon to Relipoietin had 67 files reviewed.

The pharmacy daily activity register was used to obtain names of patients who were on Recormon + Venofer since August 2008 and were changed to Relipoietin + Ferrose sucrose as from August 2014. The list of patient numbers was provided to the person in-charge of records department at KNH with a request for retrieval of the files. The patient file number was recorded in a sampling sheet and universal sampling technique was applied. The retrieved files were then reviewed by the investigator to find out if they meet the inclusion criteria. Any files not meeting the inclusion criteria were rejected. Both the patient numbers of the rejected files and the reason for rejection was noted.

3.5 Data Collection

A pharmacy record was used to obtain demographic data of the patients who were on Relipoietin and Ferrose sucrose. A pre-tested and validated data collection tool (Appendix 5) was used to collect data. The following was obtained from review of the medical records of patient files**:** demographic data (age and sex), history/etiology of renal disease, date of start of replacement therapy, dose and frequency of administration, hemoglobin level, history and frequency of dialysis, co-morbidities and concomitant use of other drugs. Data on dependent and independent variables of interest (Section 3.5.1) was also collected. The researcher personally did data abstraction.

3.5.1 Variables

Dependent variables; Hemoglobin level in g/dl, Number of hospitalizations, Mortality rate, Need for blood transfusion.

Secondary independent variable; Missed doses, type of injection/treatment given.

3.5.2 Outcomes

Primary outcome of interest

Change in hemoglobin by ±0.5g/dl over a period of six months.

Secondary outcome of interest

Changes in frequency of hospitalizations change in mortality rate after change over to current products, number of anemia events during therapy, number of transfusions during therapy and maintenance of hemoglobin levels > 11g/dl for at least 3 months.

3.6 Data Management and Quality Assurance

The data collection tool was pre-rested on ten patients who were being prepared for renal transplant in February 2015 and who were on Relipoietin and Ferrose at the renal unit in KNH. All relevant data was collected and recorded in the data collection tool, whereby any errors and omissions were noted and corrected.

All outcomes variables and covariates were recorded in the standardized data collection tool on a daily basis and back up were done regularly. A statistician was selected and assigned quality assurance, data verification and data analysis. National and international data protection laws as well as guidelines on retrospective studies were followed.

3.7 Data analysis

A data base of the data collected was created using Epi Info version 7. Descriptive and inferential data analysis was done using Statistical Package for the Social Sciences (SPSS) version 20 SPSS. Summary statistics were determined for the various variables and were presented as means, medians, standard deviation, ranges and percentiles, as appropriate. Inferential and descriptive statistics was derived from the data, and the significance level was set at 0.05. Bivariate analysis and multivariate logistic regression was done.

3.8 Study limitations

Confounders like severity of anemia, duration of use of ESA products, concomitant use of other drugs, co-morbidities and age (Older patients vs. younger patients). These were handled during analysis where stratification was done.

Time was a limitation in the sense that patients needed to be followed up for a longer duration to be able to get conclusive evidence for comparisons as opposed to few months that had elapsed after the regimen changes.

The study was also limited by poor record keeping as well as missing data.

3.9 Ethical considerations

Ethical approval was granted by Kenyatta National Hospital/University of Nairobi Ethics and Research Committee (KNH/UON-ERC)-**P29/01/2015**

Patient names were not included in the data collection form. Patients were assigned study numbers in the data collection form instead of their hospital number. Review of patient files was done within the KNH records department to ensure confidentiality. There were no direct benefits or risks to the patients during the study.

3.10 Data dissemination plan

The findings of the research will be communicated to the KNH-Medicine and Therapeutics committee through the pharmacy secretariat upon completion of the study. The same findings will be presented to relevant departments such as the Pharmacy-HOPAK (Hospital Pharmacists/pharmaceutical technologist Association of Kenya) and Medicine departments in form of Continuous Medical Education (CME) presentations to the staff in these departments.

A copy of final thesis book and soft copy will be submitted to Pharmacy and Medical School Libraries as well as the Pharmacology and Pharmacognosy Department to allow access by students and faculty members at the University of Nairobi.

A manuscript will be prepared and published in a peer-reviewed open access biomedical journal to facilitate easy access through the internet. A manuscript will also be provided to the education committee of the Pharmaceutical Society of Kenya for publishing in the Pharmaceutical Journal of Kenya.

CHAPTER 4: RESULTS

4.1 Preamble

This chapter focuses on the findings of the research. The data is summarized into tables of frequencies, percentages, bar graphs, pie charts mean, median and p-values. The results are organized based on baseline characteristics (demographic factors, diagnosis and stage of renal disease), cause of renal disease & co-morbidities and medication used by the patients.

For the purposes of the presentation and discussion of the results of this study, the "Recormon-Recormon" arm refers to the study arm in which patients were on Recormon and Venofer throughout the study period - they were not switched in August 2014, while the "Recormon-Relipoietin" arm refers to the study arm in which patients were switched from Recormon and Venofer to Relipoietin and Ferrose in August 2014.

4.2 Baseline characteristics

4.2.1 Demographic factors

Baseline characteristics of the study participants in both arms are shown in Table 6. Overall the median age was 52 years (range 18-84). In the Recormon-Recormon arm (n=73), 59.7% were above 50 years (n=43) and 65.8% were males (n=48). In the Recormon-Relipoietin arm (n=67), 41.8% were above 50 years (n=28) and 69.7% were males (n=46). In both arms (N=140) 51.1% were aged 50 years and above 4.3% were below 25 years (n=6).

4.2.2 Diagnosis and Stage of Renal Disease

A diagnosis of CKD was made in 70 % of all the population studied (n=98) while 30% had ESRD (n=42). CKD is defined as abnormalities of kidney structure or function, present for > 3 months, with implications for health. CKD is classified based on cause, GFR category, and albuminuria category (CGA classification).

A majority of the patients were in stage 4 renal disease 67.4% (n=89), while stage 5 disease accounted for 29.5% (n=39) and stage 3 disease accounted for 3% (n=4) (Table 6). Kidney Disease Improving Global Outcomes (KDIGO) classifies the stages of kidney disease based on GFR as follows: stage 1 is classified as GFR (>90) normal or high GFR; stage 2 (60-89) mildly

decreased; stage 3 is classified into 3A (45-59) and 3B (30-44) moderately reduced kidney function, stage 4 (15-29) severely reduced kidney function and stage 5(<15) as very severe, or end stage renal disease (renal failure) (3).It was observed that all the participants in the study were in stages 3-5.

Table 6: Baseline Characteristics of the Study Participants

		Arm		
		Recormon-Recormon Frequency (%)	**Recormon- Relipoietin** Frequency (%)	**All**
Sex	Male	48(65.8)	46(69.7)	94(67.6)
	Female	25(34.2)	21(30.3)	46(32.4)
Age group	18-25	0(0)	6(9.0)	6(4.3)
	26-35	7(9.7)	16(23.9)	23(16.5)
	36-50	22(30.6)	17(25.4)	39(28.1)
	>50	43(59.7)	28(41.8)	71(51.1)
Diagnosis	CKD	51(69.9)	47(70.1)	98(70.0)
	ESRD	22(30.1)	20(29.9)	42(30.0)
Stage of renal disease	3	3(4.3)	1(1.6)	4(3.0)
	4	52(75.4)	37(58.7)	89(67.4)
	5(ESRD)	14(20.3)	25(39.7)	39(29.5)

4.2.3 Cause of renal disease and co-morbidities

Hypertension (HTN) was the most prevalent cause of renal disease representing 33.3 % of the studied patients (n= 87), diabetes mellitus (DM) accounted for 30.7% (n= 80). Patients with both HTN and DM accounted for 10.0% (n= 26) while 16 patients had renal disease attributable to chronic glomerulonephritis (CGN) representing 6.1%. The other 8.4% of the patients had renal disease resulting from various etiologies including CGN with Hypertensive Heart Disease, Rapidly Progressive Glomerular Nephritis and Pre-Eclamptic Toxemia. These were grouped together as other causes, (n= 22) as shown in Figure 1 below. Comorbid conditions included were HIV which accounted for 8.4% (n=22) and cancer 3.1% (n=8).

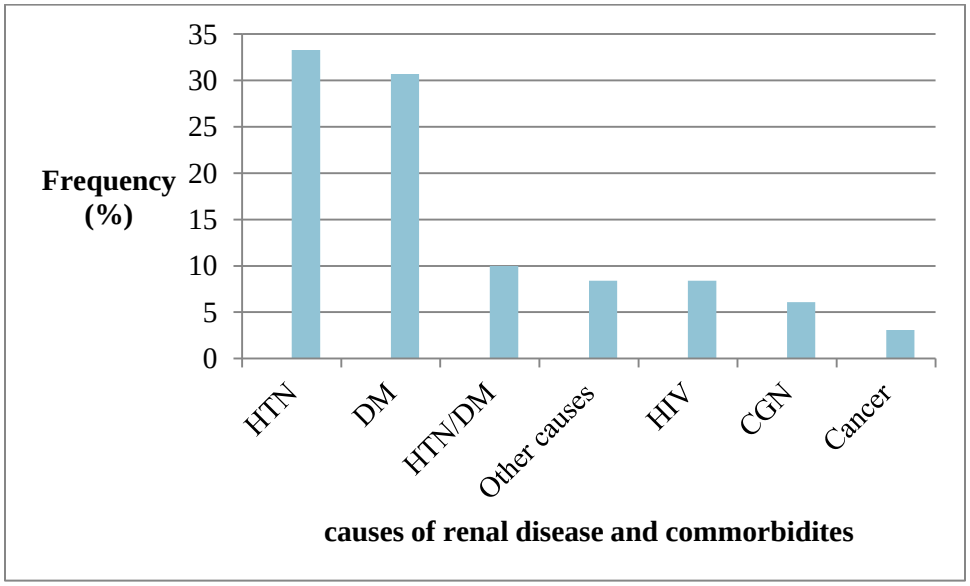

Figure 1: Cause of renal disease and other co-morbidities

4.2.4 Other medication used by the patients

Among the study population, patients were put on other prescription drugs to manage comorbidities in addition to the study medications. Each of the other prescription drugs a patient was put on was counted as a separate prescribing instance. A total number of 248 prescribing instances were encountered. Anti-hypertensive drugs accounted for 55.3% (n=161). Figure 2 below shows the distribution of the other prescription drugs.

Anti- diabetic drugs accounted for 28.5% of all medications used (n=83) while antiretroviral drugs accounted for 6.9% (n= 20). Anti-infectives, neuroleptics, anticoagulants, supplements and lipid lowering drugs were categorized as others and accounted for 9.3% (n= 27)

In the anti-hypertensive category, calcium channel blockers N=73 were prescribed in most instances, which were nifedipine (39.3%) n=55 and amlodipine (12.9%) n=18. The angiotensin receptor blocker losartan accounted for 17.9% (n=25). The rest of the anti-hypertensive drugs were beta blockers (n=23), angiotensin converting enzyme inhibitors (n=15), smooth muscle relaxants (n=15), alpha adrenergic receptor blockers (n=7), potassium sparing diuretics (n=2) and a diuretic (n=1).

Most prescribed anti diabetic drug was insulin injection (Mixtard) n=63,

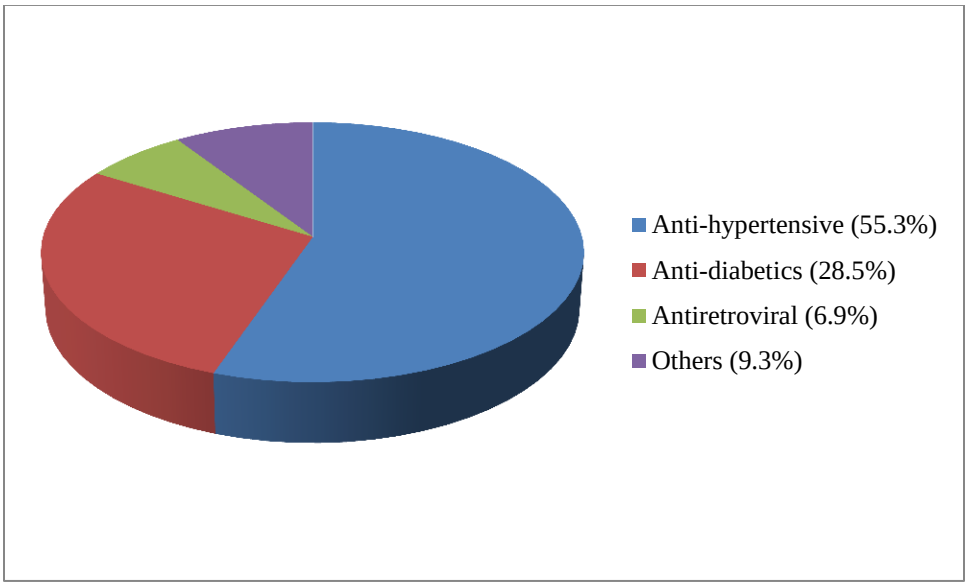

Figure 2: A chart of other medication used by patients

4.3: Effects of replacement of Recormon and Venofer injections with Relipoietin and Ferrose sucrose injections on the levels of hemoglobin

The effect of study drugs on hemoglobin levels in the entire population was analyzed then stratified between the arms. The mean changes in hemoglobin levels in each of the arms based on the diagnosis, demographic characteristics, clinical characteristics and other medications used to manage comorbidities were also analyzed using paired t- test and bivariate analysis.

A change in hemoglobin concentrations is defined as a change (either an increase or decrease) in mean hemoglobin by ±0.5 g/dl. This cut off has been used in previous comparative studies, such as the study by Saltissi *et al* (1998) that compared the effects of single versus divided doses of parenteral iron for functional iron deficiency in hemodialysis patients [72].

4.3.1: Overall changes in hemoglobin levels

In the study population, 58.6% of patients had an increase in hemoglobin (n=82) while 41.4% (n=58) had hemoglobin levels either decreasing or unchanged (Table 7)

Table 7: Changes in hemoglobin levels

	Frequency (%)
HB decreased or did not change	58(41.4)
HB increased	82(58.6)

4.3.2: Changes in hemoglobin by treatment arm

An increase in hemoglobin was observed in a higher proportion of the patients that were in the Recormon-Recormon arm 63.2% (n=48) compared to the patients in the Recormon-Relipoietin arm 53.1% (n=34). However these proportions was not significantly different (P = 0.38) (Table 8).

Table 8: Effect of drugs on Hb rise according to the arm

	Arm		
	Recormon-Recormon Frequency (%)	Recormon-Relipoietin Frequency (%)	P value
HB decreased or did not change	28(36.8)	30 (46.9)	0.38
HB increased	48(63.2)	34 (53.1)	

4.3.3 Hemoglobin level changes by diagnosis

The levels of hemoglobin in patients diagnosed with CKD increased in 55.2 % (n=53) of the cases while in those diagnosed with ESRD the Hemoglobin levels increased in 61.5 % (n=24) of the cases (p = 0.50). The changes in hemoglobin levels did not vary significantly with diagnosis (P = 0.50) (Table 9).

Table 9: Relationship between hemoglobin level changes and the diagnosis

	Diagnosis		
	CKD	ESRD	
	Frequency (%)	Frequency (%)	P value
HB decreased or did not change	43(44.8)	15(38.5)	0.50
HB increased	53(55.2)	24(61.5)	

4.3.4: Hemoglobin level changes by diagnosis, stratified by treatment arm

Stratification according to treatment arms showed that, for both the Recormon-Recormon and the Recormon-Relipoietin arms, a higher proportion of the patients with ESRD showed an increase in Hb compared to the patents with CKD, i.e. 66.7% (ESRD) compared to 58.0% (CKD) in the Recormon-Recormon arm, and 55.6% (ESRD) compared to 52.2% (CKD) in the Recormon-Relipoietin arm. However, these proportions were not significantly different (Table 10).

The highest proportion of patients with an increase in Hb was observed among the patients in the Recormon-Recormon arm and who had ESRD n=14 (66.7%). The levels of hemoglobin either decreased or did not change in 42 % (n=21) of the patients with CKD in Recormon-Recormon arm, compared to 47.8 % (n=22) of the patients with CKD in Recormon-Relipoietin arm.

Table 10: Relationship between hemoglobin level changes and diagnosis, stratified per treatment arm

	CKD	ESRD	
	Frequency (%)	Frequency (%)	P value
Recormon-Recormon arm			
Hb decreased or did not change	21(42.0)	7(33.3)	0.50
Hb increased	29(58.0)	14(66.7)	
Recormon-Relipoietin arm			
Hb decreased or did not change	22(47.8)	8(44.4)	0.80
Hb increased	24(52.2)	10(55.6)	

4.3.5: Mean Hemoglobin levels before and after the switch

Data was normally distributed hence mean reported. The mean Hb levels for the patients on Recormon-Relipoietin arm (n=67) were compared before and after the switch from Recormon and Venofer to Relipoietin and Ferrose.

For these patients on Recormon-Relipoietin arm, the switch from Recormon and Venofer to Relipoietin and Ferrose was done in August 2014. Therefore, Hb determinations before August 2014 were indicative of Hb levels while on Recormon and Venofer, whereas Hb levels determined from October 2014 provided Hb levels while on Relipoietin and Ferrose.

The period August to October 2014 was considered a sufficiently long "crossover period" from Recormon to Relipoietin to allow for the fading of the effects of Recormon and the full effects of Relipoietin to be realized. Hb levels during this crossover period were not considered for analysis.

Therefore, mean Hb before August 2014 and after October 2014 was calculated for each patient in the Recormon-Relipoietin arm. Each mean Hb concentration was calculated using Hb levels determined on three separate occasions. The overall group means Hb for the Recormon-Relipoietin arm was then calculated by averaging all the individual patient mean Hb concentrations. This was done for before and after the switch.

The Recormon-Relipoietin group mean Hb while on Recormon was 8.60 g/dl (SD: 1.96). This value decreased marginally to 8.59 g/dl (SD: 1.62) when the same patients were switched to Relipoietin (Table 11)

Table 11: Mean Hemoglobin levels before and after the switch

	Mean	**N**	**Std. Deviation**
Mean HB while on Recormon	8.60	67	1.96
Mean HB while on Relipoietin	8.59	67	1.62
Mean difference (Mean HB while on Recormon - Mean HB while on Relipoietin)	0.01 (95%CI: -0.26, 0.28)	67	1.07

The difference in the Recormon-Relipoietin group mean hemoglobin while on Recormon and while on Relipoietin was 0.01 (95%CI: -0.26, 0.28) (Table 11) and this difference was not statistically significant (P = 0.94). We infer that the patients did not have significantly higher mean hemoglobin levels while on Recormon than when switched to Relipoietin.

4.3.6: Distribution of mean hemoglobin while on Recormon and Relipoietin

Figure 3 below shows the distribution of the individual mean Hb while on Recormon in relation to mean Hb while on Relipoietin. The scatter plot and the imposed trend line show a positive linear correlation between mean Hb while on Recormon and mean Hb while on Relipoietin.

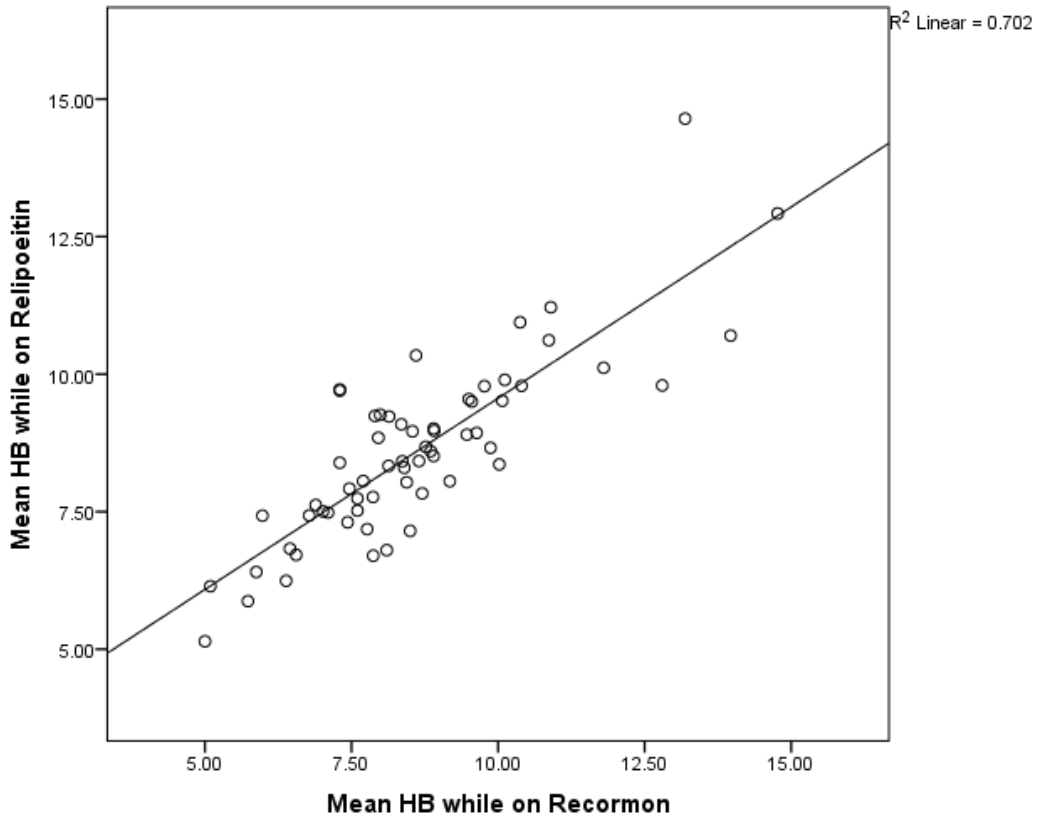

Figure 3: Mean hemoglobin concentration while on Relipoietin against mean hemoglobin concentration while on Recormon

4.3.7 Mean Hb concentration before and after switch, stratified by gender

The difference between mean hemoglobin concentration for male patients when they were on Recormon and when they were on Relipoietin (n=46) was -0.10 g/dl (95% CI: -0.44, 0.25; P= 0.58), indicating a small but non-significant drop in hemoglobin concentration for male patients after the switch from Recormon to Relipoietin.

However, the mean hemoglobin concentration for female patients increased marginally by 0.02 g/dl (95%CI: -0.28, 0.71; P= 0.38) for those patients switched from Recormon to Relipoietin (n=21) indicating a small but non-significant increase in hemoglobin concentration.

Therefore, the global effect of switching from Recormon to Relipoietin did not have a statistically significant effect on mean hemoglobin levels in patients as shown in Table 12 below.

Table 12: Mean difference in Hb stratified by gender

Sex	Mean difference in HB	Std. Deviation	95% CI		T	P value
			Lower	Upper		
Male	-0.09	1.08	-0.44	0.25	-0.56	0.58
Female	0.21	1.06	-0.28	0.71	0.90	0.38

4.3.8: Distribution of mean hemoglobin while on Recormon and Relipoietin, by gender

Figure 4 below shows the association between mean Hb while on Recormon in relation to mean Hb while on Relipoietin for the male and female gender. The scatter plots and the imposed trend lines indicate a strong positive linear correlation. It implies that Mean Hb levels while on Relipoietin were correspondingly higher among those with higher mean Hb levels while on Relipoietin regardless of the genders.

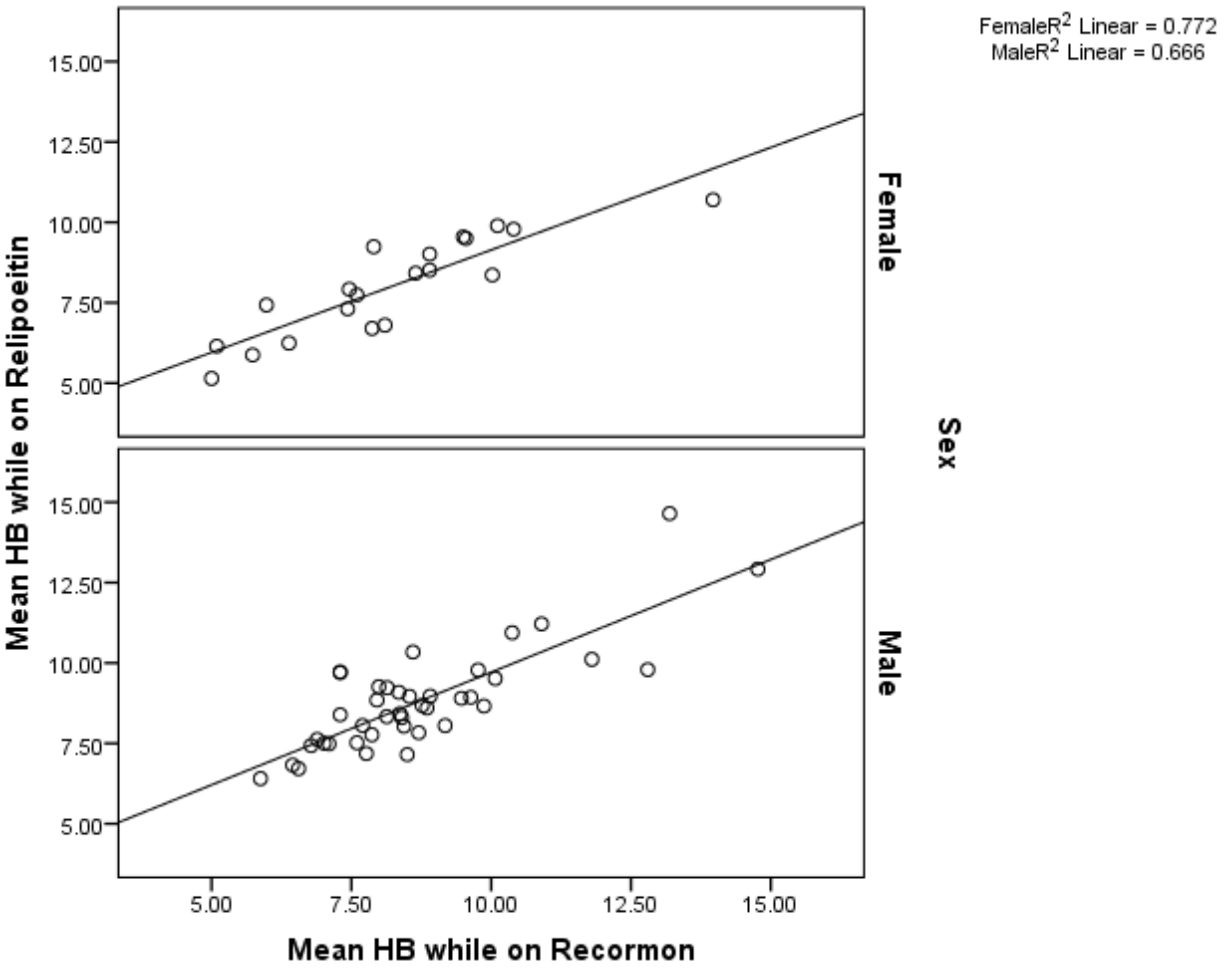

Figure 4: A plot of mean difference in hemoglobin while on Recormon and Relipoietin split according to gender

4.3.9 Mean difference according to baseline characteristics and causes of renal disease

Differences in mean hemoglobin were compared across various patient characteristics determined for the Recormon-Relipoietin arm (Table 13). The stage of renal disease at diagnosis was found to be significantly associated with mean difference in hemoglobin (P = 0.01). Patients in stage 3 renal disease had a significant decrease in Hb levels.

Table 13: Differences in Mean Hb levels for the Recormon-Relipoietin arm in relation to the baseline characteristics and causes of renal disease

Variable	Difference Mean Hb	P value
Sex		
Male	-0.09	0.30
Female	0.21	
Age group		
18-25	0.72	0.28
26-35	-0.30	
36-50	-0.09	
>50	0.12	
Diagnosis		
CKD	0.04	0.78
ESRD	-0.05	
Stage of renal disease		
3	-3.02	**0.01**
4	0.50	
5(ESRD)	0.76	
Hypertension (HTN)		
No	0.06	0.62
Yes	-0.09	
Diabetes (DM		
No	-0.01	0.75
Yes	0.12	
HTN/DM		
No	0.12	0.13
Yes	-0.39	
Rapidly Progressive (RPGN)		
No		
Yes	0.03	0.50
	-0.50	
Chronic-Glomerulonephritis (CGN)	-0.03	0.39
No	0.37	
Yes		
CGN/Hypertensive-Heart Disease (HHD)		0.54
No	0.02	
Yes	-0.65	

4.3.10 Evaluation of maintenance of hemoglobin above 11g/dl

A hemoglobin concentration of 11-12g/dl is desirable target for the management of patients with renal anemia. In both treatment arms, the number of patients with at least three Hb values sustained above 11g/dl over at least three months were determined and compared. The Recormon-Relipoietin arm had a significantly higher proportion of patients with sustained hemoglobin levels equal to or above the target as compared to the Recormon-Recormon arm, i.e. 61.2% (n=41) compared to 41.1% (n=30), respectively (p=0.02). This is shown in Table 14.

Table 14: Evaluation of hemoglobin levels in the arms

		Arm		
		Recormon-Recormon Frequency (%)	Recormon-Relipoietin Frequency (%)	P value
HB values	**<11g/dl**	43(58.9)	26(38.8)	**0.02**
	≥11g/dl	30(41.1)	41(61.2)	

4.4: Influence of demographics, clinical characteristics, other medication and missed doses on changes in hemoglobin

4.4.1: Bivariate analysis

Bivariate analysis showed that patients in stage 3 renal disease were more likely to have a decrease or no change in their hemoglobin levels (p = 0.02), (Table 15). However, this observed association could be an artefact arising from the small number of patients (n=4) with stage 3 renal disease, all of whom showed a decrease or no change in their hemoglobin levels.

Table 15: Effect of study medication on Hb levels in relation to demographics and clinical characteristics.

		Effect of study drug on Hb						
		Hb decreased or did not change		Hb increased				
		N	%	N	%	OR	95% CI	P value
Sex	Male	40	44.4	50	55.6			0.70
	Female	18	40.9	26	59.1			
Age group	18-25	3	60.0	2	40.0	1.8	0.25 – 12.99	-
	26-35	10	45.5	12	54.5	2.6	0.38 – 17.31	0.93
	36-50	14	36.8	24	63.2	2.0	0.31 – 12.42	0.60
	>50	30	43.5	39	56.5			0.79
Diagnosis	CKD	43	44.8	53	55.2	1.3	0.61 – 2.78	0.50
	ESRD	15	38.5	24	61.5			
Stage of renal failure	3	4	100.0	0	.0	-	-	**0.02**
	4	34	40.0	51	60.0	0.9	0.40 – 1.93	0.74
	5	14	36.8	24	63.2	-	-	-
Hypertension (HTN)	No	34	45.9	40	54.1			0.44
	Yes	24	39.3	37	60.7			
Diabetes (DM)	No	45	44.6	56	55.4			0.52
	Yes	13	38.2	21	61.8			
HTN/DM	No	45	41.3	64	58.7			0.42
	Yes	13	50.0	13	50.0			
Rapidly progressive glomerulonephritis (RPGN)	No	57	42.9	76	57.1			0.84
	Yes	1	50.0	1	50.0			
Chronic glomerulonephritis (CGN)	No	53	42.4	72	57.6			0.64
	Yes	5	50.0	5	50.0			
CGN/Hypertensive heart disease (HHD)	No	58	43.6	75	56.4			0.22
	Yes	0	.0	2	100.0			
End stage renal disease (ESRD)-CGN	No	54	45.4	65	54.6			0.12
	Yes	4	25.0	12	75.0			
ESRD-HTN	No	50	44.2	63	55.8			0.49
	Yes	8	36.4	14	63.6			

4.4.2: Stratification by treatment arms

Further analysis on the effects of stage of renal disease on hemoglobin change through stratification by treatment arms revealed that 3 of the 4 patients with stage 3 renal disease were in the Recormon-Recormon arm. No significant association between stage of renal disease and change in Hb was observed among males and females for the stage 4 and stage 5 patients (Table 20, **Appendix 1**).

4.4.3: Hb changes in relation to other medications used to manage comorbidities.

Analysis done based on the other medications patients were using showed that a significantly higher proportion of patients who were not using atenolol (i.e. atenolol-free patients) had an increase in hemoglobin n=75 (60.5%) compared to those using atenolol n=2 (18.2%) (p = 0.01). Of the patients using atorvastatin N=19, n=15 (78.9%) had increase in their hemoglobin levels (p = 0.04) (Table 21, **Appendix 2)**

4.4.4: Stratification by treatment arms

Stratification by treatment arm showed that, in the Recormon-Recormon arm, a significantly higher proportion of atenolol-free patients had an increase in hemoglobin (64.6%) compared to those using atenolol (35.4%) (p = 0.02). This association was not observed in the Recormon-Relipoietin arm (Table 22, **Appendix 3**).

4.4.5: Hb change by comorbidities

The levels of hemoglobin increased in 68.2% (n=15) of patients having HIV concurrently and in 37.5% (n=3) of cancer patients. However there was no statistically significant association between changes in levels of hemoglobin and comorbidities, as shown in Table 16 below.

Table 16: Effect of study drugs on Hb rise according to comorbidities

Variable		Effect of drug on Hb			
		Hb decreased or did not change Frequency (%)	Hb increased Frequency (%)	OR (95% CI)	P value
HIV	Yes	7(31.8)	15(68.2)	0.57 [0.21 – 1.50]	0.25
	No	51(45.1)	62(54.9)		
Cancer	Yes	5(62.5)	3(37.5)	2.33 [0.53-10.16]	0.25
	No	53(41.7)	74(58.3)		
Other comorbidities	Yes	1(50.0)	1(50.0)	1.33 [0.08-21.77]	0.84
	No	57(42.9)	76(57.1)		

4.4.6: Stratification by treatment arms

Most patients with co-morbidities (cancer, HIV or others) and whose hemoglobin increased were on the Recormon–Recormon arm. However, this proportion was also not significantly higher than for the Recormon-Relipoietin arm, as shown in Table 23 **(Appendix 4**).

4.4.7: Determining the effect of missed doses in hemoglobin levels

A missed dose is defined as an occurrence where a patient does not observe completely and in a timely manner the drug regimen prescribed by the health care provider. For the purpose of this study, a missed dose means missing to take EPO drug at the specified time and duration continuously for more than 2 months. The total number of patients who missed the above doses as defined was N=68. Out of these, the proportion of patients with decreased or unchanged Hb levels was 73.5% (n=40), and this was significantly higher than those who had an increase in Hb (p=0.02), as shown in Table 17 below. Five patients had missed their EPO dose for less than a month (data not shown).

Table 17: Effect of missed doses on levels of hemoglobin

	Missed doses		
	No	Yes	
	Frequency (%)	Frequency (%)	P value
HB decreased or did not change	26(38.8)	40(73.5)	**0.02**
HB increased	41(61.2)	28(26.5)	

4.4.8: Logistic regression analysis

Logistic regression revealed that the independent predictors of increased hemoglobin levels were patients who were not using atenolol [OR 6.4 (1.3-32.2)] p value=0.02 and those who had CKD [OR 2.3 (1.0-5.2)] p value=0.04 as shown in Table 18 below.

Table 18: Predictors of increased HB levels

	Coefficient	**S.E.of coefficient**	**OR**	**95% C.I. for OR**		**P value**
				Lower	Upper	
Arm	-0.57	0.41	0.56	0.25	1.26	0.16

ESRD	0.59	0.41	1.81	0.82	4.01	0.14
CKD	0.84	0.42	2.31	1.02	5.22	**0.04**
Atenolol-free	1.86	0.82	6.43	1.28	32.21	**0.02**
Atorvastatin use	0.89	0.70	2.43	0.62	9.51	0.20

4.5: Analysis of blood transfusion, hospital admissions and mortality rate

4.5.1: Hospital admissions and blood transfusion and mortality

The need for blood transfusion, rate of hospitalizations and mortality were analyzed for nine months prior to August 2014 (November 2013 – July 2014) and for nine months after August 2014 (September 2014 – May 2015) corresponding to the study period for the two arms.

In the first nine months, the requirement for blood transfusion, the rates of hospitalizations and mortality were almost similar between the two arms, while in the second nine months after August 2014, patients who were on the Recormon-Relipoietin arm required more blood transfusions (55.2% vs. 44.8%), had a higher hospital admissions rate (54.8% vs. 45.2%) and higher mortality rate (62.5% vs. 37.5%) compared to patients on the Recormon- Recormon arm - Table 19 below. While the differences in these parameters were notable it was not statistically significant.

Table 19: Evaluation of hospital admissions, need for blood transfusion and mortality per arm

Arm	**Nov 2013 – July 2014 (Recormon period)**	**Sept 2014 – May 2015 (Relipoietin period)**		
	Frequency (%)	Frequency (%)	OR [95% CI]	P value

Recormon-	Transfusion	14(58.3)	10(41.7)	1.7[0.58 -5.14]	0.33
Recormon	Hospitalizations	27(54)	23(46)	1.4[0.67-3.01]	0.35
	Mortality	7(53.8)	6(46.2)	1.9[0.44-8.61]	0.38
Recormon	Transfusion	13(44.8)	16(55.2)		
Relipoietin	Hospitalizations	28(45.2)	34(54.8)		
	Mortality	6(37.5)	10(62.5)		

CHAPTER 5: DISCUSSION, CONCLUSION AND RECOMMENDATIONS

In this chapter, study findings are discussed and conclusions are drawn from the findings. Recommendations have been made based on the study findings and conclusions drawn.

5.1 Discussion

In this study, one hundred and forty patients (46 female, 94 male) with chronic renal failure and anemia, aged 18 to 84 years of (mean age 52 ±15.49) were enrolled and this is comparable to a study done to clinically assess the results of treatment of patients with renal anemia by epoietin-beta [62], however the present study had more male than female participants. The study

population comprised of 4.3% participants aged between 18 and 25, 16.5 % between 26 and 35 while a majority 79.2% was above 36 years of age.

Hypertension and diabetes mellitus accounted for approximately 80% of the causes of renal disease which is comparable to a previous study carried out in Canada [64]. Major anti-hypertensive drugs that were used to manage hypertension in these patients were calcium channel blockers (CCBs) nifedipine and amlodipine and angiotensin receptor blocker losartan while for diabetes mellitus most patients were in insulin injection (Mixtard). Angiotensin-converting enzyme inhibitors (ACEIs) such as captopril and enalapril and angiotensin receptor blockers (ARBs) such as Losartan have been shown to be renoprotective in diabetics with proteinuria and chronic kidney disease (CKD) and recommended as first-line treatment for patients with diabetes, hypertension, and micro albuminuria. [65]. The 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults recommends the use of ACEIs or ARBs alone in blacks as first line treatment as this has been shown to delay the progression to ESRD. However, other studies have shown that ACEIs and ARBs can contribute to anemia in CKD patients. Evidence suggests that dialysis patients treated with ACEI and ARB have slightly lower hematocrits than those not on these agents [65, 66]. The contradictory findings from clinical studies on the use of ACEIs and ARBs make it difficult for physicians to adhere to existing treatment recommendations in these patients.

In this study, majority of the patients were being managed with CCBs rather than ARBs or ACEIs as their first line treatment. A study conducted by Bryan *et al* on Calcium channel blocker use and mortality among patients with end-stage renal disease showed that after controlling for known risk factors and potential confounders, CCBs were found to be associated with a lower risk of mortality among ESRD patients [73]. The 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults Report from the Panel Members Appointed to the Eighth Joint National Committee reported that in the black hypertensive population, including those with diabetes, a calcium channel blocker or thiazide-type diuretic is recommended as initial therapy [66].

All patients with HIV were on abacavir, lamivudine and efavirenz. This regimen was appropriate for the study population as it was free of zidovudine, which causes anemia. A Randomized, Pilot Trial by Laura Albini *et al* showed that ATV/r plus tenofovir caused greater GFR decreases compared with EFV [74] Another study by Frank *et al* demonstrated that urinary excretion of retinol-binding protein and β-2 microglobulin increased significantly more in the Tenofovir/Emtricitabine arm compared with the abacavir/lamivudine arm [75]. Abacavir/lamivudine/efavirenz combination had no specific contraindication in renal failure and CKD.

ESA use in patients with renal anemia is indicated to improve quality of life and decrease morbidity and mortality [61]. The effect of EPO is measured by assessing a patient's hemoglobin level, which should be checked at least monthly at the start of treatment, and once every three months when the patient is stable. This is not the case at KNH as patients are deemed too economically disadvantaged to afford monitoring their Hbs monthly or even quarterly.

In this study, 58.6% of the total patients studied had their Hb increase, with majority from Recormon-Recormon arm (63.2%) compared to the Recormon-Relipoietin arm (53.1%). However, this difference was not statistically significant, which implies that there was no significant increase in hemoglobin levels in patients in either arm and that biosimilar products were as comparatively effective as originator products.

This is a similar finding to a previous study done in Germany that assessed the therapeutic equivalence of epoetin zeta and epoetin alfa for correction of hemoglobin (Hb) concentration in patients with anemia and CKD stage 5 maintained on hemodialysis. The study concluded that Epoetin zeta, administered intravenously, is therapeutically equivalent to epoetin alfa in the correction of low Hb concentration in patients with CKD undergoing hemodialysis [67].

One of the factors that could influence the response to EPO (both Recormon and Relipoietin) is the development of tolerance. Tolerance is said to occur when the effectiveness of a drug decreases with continued use over long duration time. Pharmacodynamics tolerance occurs when the same concentration at the receptor site results in a reduced effect with repeated exposure.

This might have been the case at KNH as most patients had used erythropoietin (Recormon + Venofer) for at least two years prior to the study at a sustained twice weekly dosage (2000i.u). Tolerance may also be caused by pharmacokinetic factors, such as increased drug metabolism, that decrease the concentrations achieved with a given dose.

This study found that, though changes in hemoglobin levels did not vary significantly with diagnosis (P = 0.501), a higher proportion (61.5%) of patients diagnosed with ESRD had an increase in their hemoglobin compared to those diagnosed with CKD (55.2%). KDOQI defines stages of renal disease based on glomerular filtration rate (GFR). Stage 5 renal disease, or ESRD, is the most severe/advanced form of renal disease, and is characterized by GFR <15 mL/min). This study therefore demonstrated that patients with advanced renal disease (stage 5) could possibly benefit more from erythropoietin replacement therapy, which is consistent with other studies done in UK and USA [68]. This is probably so because hemoglobin deficiency is greater in advanced renal disease, and the positive effects of replacement therapy are more pronounced.

The change in mean Hb was also analyzed according sex and the hemoglobin rise was almost equal in both arms with female patients having a slight increase in mean Hb. Male patients showed a slight decrease in mean Hb. This could be explained by the fact that majority of the male participants were older than the female participants.

The mean difference in Hb was associated with stage of renal failure, where patients in stage 5 (ESRD) had most increase while those in stage 3 had a slight decrease in their mean Hb. This is contrary to the expectation that there would be a considerable increase in Hb levels at stage 3 but could be explained by the fact that the patients in stage 3 included in the study were only 4 and hence may not have been representative of expected response in patient population at stage 3 disease.

The National Kidney Foundation Kidney Disease Outcome Quality Initiative (KDOQI) recommends targeting Hb between 11.0 and 12.0 g/dl. In other words, Hb maintained between 11-12g/dl is desirable for patients on erythropoietin treatment, though evidence suggests that only 30 % of patients fall within this range at any point in time [63].

In the current study, a higher proportion of patients from the Recormon-Relipoietin arm (61.2%) were able to maintain their Hb above 11g/dl for a period of at least three months, compared to 41.1% of the patients on the Recormon-Recormon arm. This could be explained by the fact that prescribers had an option of letting patients with high Hbs get their EPO (Relipoietin) supply from KNH pharmacy and advice those with low Hbs to outsource the branded EPO (Recormon) from elsewhere (outside chemists).

Patients who were atenolol-free in this study and belonged to the Recormon-Recormon arm had their hemoglobin rise significantly compared to those on atenolol. This is contrary to a previous study done in India which showed that treatment with atenolol for mild to moderate hypertension was accompanied by a significant increase in Hb and PCV level [69]. The biochemical parameters of the atenolol-free patients showed normal sodium and potassium levels; however their urea & creatinine levels were far higher than normal while average hematocrit levels were far lower than normal levels. The atenolol-free patients were however on other beta blockers such as Carvedilol and Metoprolol. This may explain why they still had an increase in Hb levels expected with atenolol, which is also a beta blocker. Beta blockers are thought to raise Hb levels as a result of the decrease in sodium and water reabsorption by decrease in sympathetic over activity and excretion of sodium and water by improvement in kidney functions, associated with beta blockers [69].

The nine patients who were on atenolol and their Hb either decreased or did not change were also either on Enalapril (ACEI) or Losartan (ARB). The two classes of drugs have been shown to decrease hemoglobin level by blocking the erythropoietic effects of angiotensin II on red cell precursors and improved renal blood flow secondary to renal efferent vasodilation, which improves oxygenation [70]. They also cause a lowering of hematocrit by inactivating the renin angiotensin system. This could also explain why the hematocrit level for the nine patients was within normal range [71]. This could therefore counteract the expected atenolol effects of increasing hemoglobin levels.

There was no statistically significant association observed between the change in levels of hemoglobin and the comorbidities which the patients had. This is possibly because the patients were under management for the comorbidities and the drugs used such as abacavir in

management of HIV had no effects on hemoglobin levels [75]. The most common cancer cases were breast, cervical prostate and lung; the drugs used to manage these cancers have direct effect on white blood cells as opposed to red blood cells and thus no direct effect on hemoglobin levels.

Most patients (73.5%) who missed their prescribed drugs for duration of more than two months continuously had their Hb decrease or not change. It's observed that missing doses was associated with negative outcomes of decrease or no changes in Hb levels. This emphasizes the importance of renal replacement drugs in the management of the anemia.

The study also demonstrated that the number of hospital admissions, mortality rate and the need for blood transfusion was higher in the Recormon-Relipoietin arm, though this was not statistically significant. This means that the effects of the biosimilar products were comparable and non-inferior to the effects of originator products. This observation is in agreement with the results of a study conducted by Ernesto Paoletti *et al* which concluded that normalization of Hb in renal patients seems to be associated with further improvement in quality of life and physical activity but with no significant differences in mortality rate and hospitalization rate [76].

5.2 Conclusion

Hemoglobin increased in patients on both treatment arms. The Recormon - Relipoietin arm patients maintained a higher hemoglobin concentration compared to the ones on Recormon - Recormon arm. There was no marked difference in terms of rate of hospitalizations, need for blood transfusion and mortality rate during both treatment periods. Atenolol free patients had significant increase in Hb and missing EPO doses affects the treatment outcome negatively.

Recormon and Relipoietin were shown to improve hemoglobin levels over time. Biosimilar agents are gaining popularity in the market today and the use of quality generic/biosimilar products has been shown to be safe, effective, efficacious and affordable. Health care providers need to be educated on the differences between original and biosimilar erythropoietin to ensure

patients with renal disease are appropriately managed particularly in terms of pharmacokinetics of the drugs, dosing schedule, storage of the drugs and monitoring the hemoglobin levels.

5.3 Recommendations

5.3.1 Recommendation for practice

Patients in KNH are deemed too poor to monitor their Hb monthly as recommended by the treatment guidelines. Treatment outcomes are therefore not clearly monitored as required. Biosimilar ESAs vary in carbohydrate structure which may occur as a result of using different cell lines during manufacturing, thus affecting the pharmacokinetic properties of the molecule and leading to a change in potency among different biosimilar ESAs. For this reason, it is recommended that clinicians monitor hemoglobin levels when:

1) Switching from an innovator to a biosimilar ESA.

2) Switching from one biosimilar ESA molecule to another.

The effect of EPO is measured by assessing a patient's hemoglobin level, which should be checked at least monthly at the start of treatment, and once every three months when the patient is stable.

5.3.2 Recommendation for research

For KNH settings, a small sample size prospective study can be carried out by enrolling the newly diagnosed renal anemia patients to either the Recormon arm or Relipoietin arm and follow them up in time for a sufficient duration to get the real world practice experience on product specific effectiveness and safety profile.

Large-sample, long-term, observational and preferably prospective/longitudinal studies of real-world practice will provide the heterogeneity and statistical power to demonstrate product-specific effectiveness and safety profiles.

REFERENCES

1. Wallace MA. Anatomy and physiology of the kidney. AORN J. 1998 Nov; 68(5):799–820.

2. Taylor, Tim. Kidneys. Inner Body: http://www.innerbody.com/image_urinov/dige05-new.html

3. Kerry W, Michael C, Sean S. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease Volume 2 | Issue 4 | August 2012□; 284-92. [Accessed 2014 Nov].

4. Edgar V. Anemia of Chronic Disease and Renal Failure: Overview, Mechanism of Anemia of Chronic Disease, Prevalence of Anemia of Chronic Disease and CKD. 2014 June

5. Health information department, KNH Nov 2014.pdf. [Accessed 2014 Nov].

6. Van Nooten FE, Green J, Brown R, Finkelstein FO, Wish J. Burden of illness for patients with non-dialysis chronic kidney disease and anemia in the United States: review of the literature. J Med Econ. 2010; 13(2):241–56.

7. Hsu C, McCulloch CE, Curhan GC. Epidemiology of anemia associated with chronic renal insufficiency among adults in the United States: Results from the third national health and nutrition examination survey. J Am Soc Nephrol. 2002 Feb 1; 13(2):504–10.

8. Locatelli F, Pisoni RL, Akizawa T, Cruz JM, DeOreo PB, Lameire NH, *et al*. Anemia management for hemodialysis patients: kidney disease outcomes quality initiative (K/DOQI) guidelines and dialysis outcomes and practice patterns study findings. Am J Kidney Dis. 2004; 44:27–33.

9. Hayat A, Haria D, Salifu MO. Erythropoietin stimulating agents in the management of anemia of chronic kidney disease. 2008 Feb; 2:195–200.

10. Jaime C, Allan J. Williams Hematology: Anemia of chronic renal failure. Free Medical Textbook. [Accessed 2014 Nov].

11. Eschbach JW, Egrie JC, Downing MR, Browne JK, Adamson JW. Correction of the anemia of end-stage renal disease with recombinant human erythropoietin. Results of a combined phase I and II clinical trial. N Engl J Med. 1987 Jan 8; 316(2):73–8.

12. Drüeke TB, Barany P, Cazzola M, Eschbach JW, Grützmacher P, Kaltwasser JP, *et al*. Management of iron deficiency in renal anemia: guidelines for the optimal

therapeutic approach in erythropoietin-treated patients. Clin Nephrol. 1997; 48(1):1–8.

13. Siyoi F, Chumo K, Njue B. Registered Human Drugs. Pharmacy and Poisons Board [Internet]. Available from: http://pharmacyboardkenya.org/?p=513

14. Liebich HG. Functional morphology of the kidney. A review of the histophysiology of the kidney glomerulus, the nephrons and the collecting tubule system. Tierärztl Prax. 1990 Apr; 18(2):109–21.

15. Preuss HG. Basics of renal anatomy and physiology. Clin Lab Med. 1993 Mar; 13(1):1–11.

16. Siamak N. Anemia symptoms and causes. [Accessed 2014 Dec]. Available from: http://www.medicinenet.com/anemia/article.htm

17. Origa R, Moi P, Galanello R, Cao A. Alpha-Thalassemia. GeneReviews). 1993.

18. Cao A, Galanello R, Origa R. Beta-Thalassemia. GeneReviews). 1993.

19. Ku E. Pathophysiology of renal anemia. Clin Nephrol. 2000 Feb; 53(1 Suppl):S2–8.

20. Nangaku M, Eckardt KU. Pathogenesis of renal anemia. Semin Nephrol. 2006 Jul; 26(4):261–8.

21. Jha V, Garcia-Garcia G, Iseki K, Li Z, Naicker S, Plattner B, *et al*. Chronic kidney disease: global dimension and perspectives. The Lancet. 2013 Jul; 382(9888):260–72.

22. Lawrence A, Kevin A, and Paul E, United States renal data system Vol 2 2009.

23. Mehdi U, Toto R. Anemia, diabetes and chronic kidney disease. Diabetes Care. 2009 Jul 1;32(7):1320–6.

24. Eric P. Nephrotic Syndrome. [Accessed 2015 Jan]; Available from: http://emedicine.medscape.com/article/244631-overview

25. New JP, Aung T, Baker PG, Yongsheng G, Pylypczuk R, Houghton J, *et al*. The high prevalence of unrecognized anemia in patients with diabetes and chronic kidney

disease: a population-based study. Diabet Med J Br Diabet Assoc. 2008 May; 25(5):564–9.

26. Naicker S. Burden of end-stage renal disease in sub-Saharan Africa. Clin Nephrol. 2010 Nov; 74 Suppl 1:S13–6.

27. Mcligeyo S, Kayima J, Were J, Ogolla James W. [Accessed 2014 Nov]. Available from: http://kapkenya.org/repository/CPDs/Conferences/Annual.2013/ pdf

28. Christensen DL, Friis H, Mwaniki DL, Kilonzo B, Tetens I, Boit MK, *et al*. Prevalence of glucose intolerance and associated risk factors in rural and urban populations of different ethnic groups in Kenya. Diabetes Res Clin Pract. 2009 Jun; 84(3):303–10.

29. Kayima K. Interlinking cardiovascular disease chronic kidney disease and obesity [Accessed 2014 Nov]. http://kapkenya.org/repository/CPDs/cardiovasculer/Kayima.pdf

30. Amador M. Anemia in chronic kidney disease. Rev Médica Inst Mex Seguro Soc. 2014 Dec; 52(6):660–5.

31. Clearing H. Anemia in Chronic Kidney Disease July 2014 [Accessed 2014 Nov]. Available from: http://kidney.niddk.nih.gov/kudiseases/pubs/anemia/

32. Rostand SG, Brunzell JD, Cannon RO, Victor RG. Cardiovascular complications in renal failure. J Am Soc Nephrol. 1991; 2(6):1053–62.

33. Gouva C, Nikolopoulos P, Ioannidis JPA, Siamopoulos KC. Treating anemia early in renal failure patients slows the decline of renal function: A randomized controlled trial. Kidney Int. 2004 Aug; 66(2):753–60.

34. Brouns R, De Deyn PP. Neurological complications in renal failure: a review. Clin Neurol Neurosurg. 2004; 107(1):1–16.

35. Cameron JS. European best practice guidelines for the management of anaemia in patients with chronic renal failure. Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc. 1999; 14 Suppl 2:61–5.

36. David W, Bertram K. Kidney disease improving global outcomes- KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease Volume 2 | Issue 4 | August 2012□; 284-92. [Accessed 2014 Dec].

37. Tilkian EE, Tzekov VD, Pandeva SM, Kumchev EP, Nikolov DG, Dimitrakov JD, *et al*. Epoetin-beta (Recormon-Roche) in the treatment of renal anemia in patients with chronic renal failure. Folia Med (Plovdiv). 2000; 42(3):11–5.

38. Rozental' RL, Zezina LI, Spudass AV. The use of recombinant erythropoietin with patients on programmed hemodialysis. Ter Arkhiv. 1991; 63(12):110–3.

39. Hahn D, Cody JD, Hodson EM. Frequency of administration of erythropoiesis-stimulating agents for the anaemia of end-stage kidney disease in dialysis patients. Cochrane Database Syst Rev. 2014; 5:CD003895.

40. Deray G. Achieving therapeutic targets in renal anaemia: considering cost-efficacy. Curr Med Res Opin. 2004 Jul; 20(7):1095–101.

41. Manley HJ, Grabe DW. Determination of iron sucrose (Venofer) or iron dextran (DexFerrum) removal by hemodialysis: an in-vitro study. BMC Nephrol. 2004 Jan 12; 5:1.

42. Eschbach JW, Abdulhadi MH, Browne JK, Delano BG, Downing MR, Egrie JC, *et al*. Recombinant human erythropoietin in anemic patients with end-stage renal disease results of a phase III multicenter clinical trial. Ann Intern Med. 1989; 111(12):992–1000.

43. Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barre PE. The impact of anemia on cardiomyopathy, morbidity and mortality in end-stage renal disease. Am J Kidney Dis Off J Natl Kidney Found. 1996 Jul; 28(1):53–61.

44. Kosch M, Bahner U, Bettger H, Matzkies F, Teschner M, Schaefer RM. A randomized, controlled parallel-group trial on efficacy and safety of iron sucrose (Venofer) vs iron gluconate (Ferrlecit) in haemodialysis patients treated with rHuEpo. Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc. 2001 Jun;16(6):1239–44.

45. Fesiuk AF, Mordik AI, Borisova EV, Borisov AV, Lovchinskiĭ EV. Use of venofer for iron deficiency correction in patients undergoing programmed hemodialysis. Ter Arkhiv. 2003; 75(8):59–61.

46. Macdougall IC, Strauss WE, McLaughlin J, Li Z, Dellanna F, Hertel J. A randomized comparison of ferumoxytol and iron sucrose for treating iron deficiency anemia in patients with CKD. Clin J Am Soc Nephrol CJASN. 2014 Apr; 9(4):705–12.

47. Aronoff GR, Bennett WM, Blumenthal S, Charytan C, Pennell JP, Reed J, *et al*. Iron sucrose in hemodialysis patients: safety of replacement and maintenance regimens. Kidney Int. 2004 Sep; 66(3):1193–8.

48. Canziani ME, Yumiya ST, Rangel EB, Manfredi SR, Neto MC, Draibe SA. Risk of bacterial infection in patients under intravenous iron therapy: dose versus length of treatment. Artif Organs. 2001 Nov; 25(11):866–9.

49. Kuriyama S, Tomonari H, Yoshida H, Hashimoto T, Kawaguchi Y, Sakai O. Reversal of anemia by erythropoietin therapy retards the progression of chronic renal failure, especially in nondiabetic patients. Nephron. 1997;77(2):176–85.

50. Rossert J, Levin A, Roger SD, Hörl WH, Fouqueray B, Gassmann-Mayer C, *et al*. Effect of early correction of anemia on the progression of CKD. Am J Kidney Dis Off J Natl Kidney Found. 2006 May; 47(5):738–50.

51. Weise M, Bielsky M-C, De Smet K, Ehmann F, Ekman N, Narayanan G, *et al*. Biosimilars—why terminology matters. Nat Biotechnol. 2011 Aug; 29(8):690–3.

52. Hörl WH. Differentiating factors between erythropoiesis-stimulating agents: An update to selection for anaemia of chronic kidney disease. Drugs. 2013 Feb; 73(2):117–30.

53. European Medical Agency, Guidelines on non clinical and clinical development of similar biological medicinal products containing recombinant erythropoietins.pdf.

54. Elliott S. Erythropoiesis-stimulating agents. [Accessed 2014 Dec]. p. 55–74. Available from: http://link.springer.com/chapter/10.1007/978-1-4419-7073-2_4

55. Toblli JE, Cao G, Oliveri L, Angerosa M. Differences between original intravenous iron sucrose and iron sucrose similar preparations. Arzneimittelforschung. 2009; 59(4):176–90.

56. Executive Board of the Health Ministers' Council for GCC States. The GCC Guidelines for Bioequivalence version 2.3 (2011)

57. Cho S-H, Lim H-S, Ghim J-L, Choe S, Kim U-J, Jung JA, *et al.* Pharmacokinetic, tolerability, and bioequivalence comparison of three different intravenous formulations of recombinant human erythropoietin in healthy Korean adult male volunteers: an open-label, randomized-sequence, three-treatment, three-way crossover study. Clin Ther. 2009 May; 31(5):1046–53.

58. Borgheini G. The bioequivalence and therapeutic efficacy of generic versus brand-name psychoactive drugs. Clin Ther. 2003 Jun; 25(6):1578–92.

59. Schellekens H. Biosimilar therapeutics—what do we need to consider? NDT Plus. 2009 Jan 1; 2(suppl 1):i27–36.

60. Jos W. R. Twisk , Applied Longitudinal Data Analysis for Epidemiology: A Practical Guide

61. Hayat A, Dhiren H *et al* Erythropoietin stimulating agents in the management of anemia of chronic kidney disease. Patient Preference and Adherence 2008:2 195–200

62. Tilkian EE, Tzekov VD, Pandeva *et al* Epoetin-beta (Recormon-Roche) in the treatment of renal anemia in patients with chronic renal failure. Folia med (Plovdiv) 2000; 42 (3): 11-5

63. McCarley P, The KDOQI clinical practice guidelines and clinical practice recommendations for treating anemia in patients with chronic kidney disease: implications for nurses Vol.33 issue 4 pages 423-426, 445

64. Malvinder S. Parmar. Chronic renal disease *BMJ* 2002;325:85–90

65. A Mohanran, Z Zhang , S Shahinfar , *et al*. The effect of losartan on hemoglobin concentration and renal outcome in diabetic nephropathy of type 2 diabetes Kidney International (2008) 73, 630–636;

66. Yannick Le Meur,Valérie Lorgeot, Lydie Comte *et al*. Plasma levels and metabolism of AcSDKP in patients with chronic renal failure: Relationship with erythropoietin requirements. Vol 38 issue 3 pages 510-517

67. Stefa Krivoshiev, Vasil V, Jacek Mariutius *et al.* Comparison of the therapeutic effects of epoetin zeta and epoetin alfa in the correction of renal anemia Volume 24, Issue 5, May 2008, pages 1407-1415

68. Sandra Ribeiro, Elísio Costa, Luís Belo *et al.* rhEPO for the Treatment of Erythropoietin Resistant Anemia in Hemodialysis Patients – Risks and Benefits:http://dx.doi.org/10.5772/52061

69. Zala AC, Kantharia ND, Malam PP, Vaghasiya KB, Soni RG, Gajera CN. Effect of atenolol on hemoglobin level in mild to moderate hypertension. Int J Basic Clin Pharmacol. (2014), [cited September 16, 2015]; 3(4): 701-705. doi:10.5455/2319-2003.ijbcp20140829

70. Mrug *et al* J. Clin. Invest. The American Society for Clinical Investigation, Inc. 0021-97, 2310–2314. Angiotensin II Stimulates Proliferation of Normal Early Erythroid Progenitors

71. Marathias K, Agroyannis B, Mavromoustakos *et al.* Hematocrit-lowering Effect Following Inactivation of Renin-Angiotensin System with Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blockers. Volume 4 (2004) issue 4 pages 483-486

72. Saltissi D, Sauvage D, Westhuyzen J. Comparative response to single or divided doses of parenteral iron for functional iron deficiency in hemodialysis patients receiving erythropoietin (EPO): Clinical nephrology 1998,Volume 49. Issue Pages 45-8.

73. Bryan.K, Danielle. G, Donald J *et al*. Calcium channel blocker use and mortality among patients with end-stage renal disease: Kidney International, Vol. 61 (2002), pp. 2157–2164

74. Albini Laura, Cesana Bruno, Mario Motta, David *et al*. A Randomized, Pilot Trial to Evaluate Glomerular Filtration Rate by Creatinine or Cystatin C in Naive HIV-Infected Patients after Tenofovir/Emtricitabine in Combination with Atazanavir/Ritonavir or Efavirenz: JAIDS Journal of Acquired Immune Deficiency Syndromes: 1 January 2012 - Volume 59 - Issue 1 - p 18–24

75. Frank A, Moyle Graeme J, Stellbrink *et al*. Randomized Comparison of Renal Effects, Efficacy, and Safety With Once-Daily Abacavir/Lamivudine Versus Tenofovir/Emtricitabine, Administered With Efavirenz, in Antiretroviral-Naive, HIV-1–Infected Adults: 48-Week Results From the ASSERT Study: JAIDS Journal of Acquired Immune Deficiency Syndromes: 1 September 2010 - Volume 55 - Issue 1 - pp 49-57

76. Ernesto. P. and Giuseppe C. Update on Erythropoietin Treatment: Should Hemoglobin Be Normalized in Patients with Chronic Kidney Disease?: J Am Soc Nephron 17: S74–S77.

APPENDICES

Appendix 1

Table 20: Stratification of the stage of renal failure by arm

		Arm							
		Recormon - Recormon				**Recormon - Relipoietin**			
		Hb decreased or did not change	**Hb increased**	**OR [95%CI]**		**Hb decreased or did not change**	**Hb increased**	**OR [95%CI]**	
		N (%)	N (%)		P value	N (%)	N (%)		P value
Stage of renal failure	3	3(100)	0(0.0)		**0.043**	1(100)	0(0.0)		0.212
	4	16(32.0)	34(68.0)	1.5 [0.42-5.02]	0.543	18(51.4)	17(48.6)	0.57 [0.20-1.64]	0.293
	5	5(35.7)	9(64.3)			9(37.5)	15(62.5)		

Appendix 2

Table 21: Effect of study drugs on Hb levels in relation to other medications

Drug		**Effect of study drug on Hb**			
		Hb decreased or did not change	**Hb increased**		
		Frequency (%)	**Frequency (%)**	**OR (95% CI)**	**P value**
Nifedipine	No	29(36.3)	51(63.8)	1.96[0.98-3.94]	0.06
	Yes	29(52.7)	26(47.3)		
Amlodipine	No	49(41.5)	69(58.5)	1.58[0.57-4.39]	0.37
	Yes	9(52.9)	8(47.1)		
Furosemide	No	57(42.5)	77(57.5)	-	0.25
	Yes	1(100.0)	0(0)		
ABC/3TC/EFV	No	52(45.2)	63(54.8)	0.52[0.19-1.45]	0.20
	Yes	6(30.0)	14(70.0)		
Carbamazepine	No	58(43.3)	76(56.7)	-	0.38
	Yes	0(0)	1(100.0)		
Septrin	No	58(43.9)	74(56.1)	-	0.13
	Yes	0(0)	3(100.0)		

Drug		**Effect of study drug on HB**			
		HB decreased or did not change	**HB increased**		
		Frequency (%)	**Frequency (%)**	**OR (95% CI)**	**P value**
Carvedilol	No	52(41.9)	72(58.1)	1.66[0.48-5.74]	0.42
	Yes	6(54.5)	5(45.5)		
Aldactone	No	57(42.5)	77(57.5)	-	0.25
	Yes	1(100.0)	0(0)		
Hydralazine	No	51(42.1)	70(57.9)	1.37[0.45-4.16]	0.57
	Yes	7(50.0)	7(50.0)		
Heparin	No	55(42.0)	76(58.0)	4.15[0.42- 40.91]	0.42
	Yes	3(75.0)	1(25.0)		
Glibenclamide	No	58(43.6)	75(56.4)	-	0.22
	Yes	0(0)	2(100.0)		
Enalapril	No	50(41.7)	70(58.3)	1.6[0.54-4.70]	0.39
	Yes	8(53.3)	7(46.7)		
Multivitamins	No	58(43.0)	77(57.0)	-	-
	Yes	0(0)	0(0)		

Drug		**Effect of study drug on HB**			
		HB decreased or did not change	**HB increased**		
		Frequency (%)	**Frequency (%)**	**OR (95% CI)**	**P value**
Atenolol	No	49(39.5)	75(60.5)	**6.89[1.43-33.23]**	**0.01**
	Yes	9(81.8)	2(18.2)		
Mixtard	No	41(41.8)	57(58.2)	1.18[0.55-2.53]	0.67
	Yes	17(5.9)	20(54.1)		
Methyldopa	No	55(42.6)	74(57.4)	1.35[0.26-6.92]	0.72
	Yes	3(50.0)	3(50.0)		
Losartan	No	45(40.9)	65(59.1)	1.57[0.65-3.74]	0.31
	Yes	13(52.0)	12(48.0)		
Atorvastatin	No	54(46.6)	62(53.4)	**0.31[0.10-0.98]**	**0.04**
	Yes	4(21.1)	15(78.9)		
Metoprolol	No	57(42.5)	77(57.5)	-	0.25
	Yes	1(100.0)	0(0)		

Appendix 3

Table 22: Stratification of medications by arm

Arm									
		Recormon - Recormon				**Recormon - Relipoietin**			
		HB decreased or did not change	**HB increased**			**HB decreased or did not change**	**HB increased**		
		N (%)	N (%)	OR [95% CI]	P value	N (%)	N (%)	OR [95% CI]	P value
Atenolol	Yes	5(83.3)	1(16.7)	9.13 [1.01-82.92]	**0.02**	4(80)	1(20)	5.08 [0.53-48.2]	0.12
	No	23(35.4)	42(64.6)			26(44.1)	33(55.9)		
Atorvastatin	No	25(44.6)	31(55.4)	0.31 [0.08-1.22]	0.08	29(48.3)	31(51.7)	2.81 [0.28-28.5]	0.37
	Yes	3(20)	12(80)			1(25)	3(75)		

Appendix 4

Table 23: Stratification of the comorbidities by arm

		Arm							
		Recormon – Recormon				**Recormon - Relipoietin**			
		Hb decreased or did not change	**Hb increased**			**Hb decreased or did not change**	**Hb increased**		
		N (%)	**N (%)**	**P value**	**OR [95%CI]**	**N (%)**	**N (%)**	**P value**	**OR [95%CI]**
HIV	Yes	4 (28.6)	10(71.4)	0.35	0.55 [0.15-1.97]	3(37.5)	5(62.5)	0.57	0.64 [0.14-2.96]
	No	24(42.1)	33(57.9)			27(48.2)	29(51.8)		
Cancer	Yes	2(40.0)	3(60.0)	0.98	1.03 [0.16-6.56]	3(100)	0(0)	0.06	-
	No	26(39.4)	40(60.60			27(44.3)	34(55.7)		
Other comorbidities	Yes	1(100.0)	0(0)	0.21	-	0(0)	1(100.0)	0.34	-
	No	27(38.6)	43(61.4)			30(47.6)	33(52.4)		

Appendix 5

Data collection form

Demographic factors

Patient number…… Sex [ ] Male [ ] Female Age (years)…….

1. Diagnosis …….
2. Stage of renal disease…….
3. Medical history and cause of renal disease

   Please tick the appropriate response

   - Hypertension (HTN)
   - Diabetes (DM)
   - HTN/DM
   - Pre -eclamptic toxemia (PET)
   - End stage renal disease (ESRD)
   - Rapidly progressive glomerulonephritis (RPGN)
   - Focal segmental/ sclerosing glomerulonephritis (FSGN)
   - Chronic glomerulonephritis (CGN)
   - CGN/Hypertensive heart disease (HHD)
   - End stage renal disease (ESRD)-CGN
   - ESRD-HTN
   - Other (please specify)…….

4. Medication history

   - Relipoietin and Ferrose:

     Dose…….

     Frequency…….

     Date started…….

   - Missed doses:

     Frequency/number of doses missed ……..

     Reasons……..

     ……

     ……

     ……

     ……

     ……

     ……

   - Other drugs

Drug	Dose	Duration

5. Renal function parameters

Calcium urea and electrolytes (CUE)……..

Serum creatinine…….

Others ……

6. Hemoglobin and other hematological measures (hematocrit)

Date TBC was done	Hemoglobin level (g/dl)	Hematocrit level (%)

7. Hospitalizations

Date	Duration	Reason(s)

8. Blood transfusions

Date	Amount (pints)	Reason(s)	Remarks/comments

9. Co-morbidities and complications

……
……
……
……
……

Appendix 6

KENYATTA NATIONAL HOSPITAL/UNIVERSITY OF NAIROBI ETHICAL AND RESEARCH COMMITTEE APPROVAL

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Ref: KNH-ERC/A/152

2nd April, 2015

Pamela N. Nambande
U51/69082/2013
Dept. of Pharmacology and Pharmacognosy
School of Pharmacy
University of Nairobi

Dear Pamela

Research Proposal: Effectiveness of (Recormon) Erythropoietin and (Venofer) Iron Sucrose Injection Compared to Biosimilar Products in Management of Renal Anaemia (P29/01/2015)

This is to inform you that the KNH/UoN-Ethics & Research Committee (KNH/UoN-ERC) has reviewed and **approved** your above proposal. The approval periods are 2nd April 2015 to 1st April 2016.

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH/UoN ERC before implementation.
c) Death and life threatening problems and severe adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH/UoN ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH/UoN ERC within 72 hours.
e) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
f) Clearance for export of biological specimens must be obtained from KNH/UoN-Ethics & Research Committee for each batch of shipment.
g) Submission of an *executive summary* report within 90 days upon completion of the study This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/or plagiarism.

For more details consult the KNH/UoN ERC website **www.erc.uonbi.ac.ke**

Yours sincerely

PROF. M. L. CHINDIA
SECRETARY, KNH/UON-ERC

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