RETROSPECTIVE ANALYSIS OF PHASE 3 CLINICAL TRIAL TO EVALUATE THE EFFICACY OF DRUG B IN ANEMIA SECONDARY TO CHRONIC KIDNEY DISEASE

INTERNSHIP PRACTICUM REPORT

Presented to the Graduate Council of the
Graduate School of Biomedical Sciences
University of North Texas
Health Science Center at Fort Worth

In Partial Fulfillment of the Requirements
For the Degree of
MASTER OF SCIENCE IN CLINICAL RESEARCH MANAGEMENT

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Fort Worth, Texas
December 2019

ACKNOWLEDGEMENTS

First, I want to say thank you to Sunbeam Clinical Research and my mentor, Dr. Sami Alam, for allowing me to work on this project and participate in all facets of clinical research. Your guidance, correction, encouragement, and insight has immensely prepared me for what I will encounter in the world of clinical research, and this internship would not have been possible without you.

I would also like to thank my major professor, Dr. Stephen Mathew, for helping me throughout the internship process and providing guidance and important information regarding the thesis. Having your help made this process an easier feat. To the other member of my advisory committee, Dr. Riyaz Basha, thank you for your constructive feedback on my research proposal and comments on the final practicum report. Your insight was helpful in completing this report.

It would be a shame if I did not acknowledge the administrators and clinical research coordinators that helped me out tremendously over the last six months with a special thank you to Mohamad Ibrahim and Aldo Aviña for their statistical insight.

Last, but not least, I would like to thank the Lord above for getting me to this place in my education. Thank you to my family and friends for their encouragement, hugs, talks, food, and always being there whenever I needed a helping hand or a shoulder to lean on. None of this would have been possible without your support, and for that I cannot express enough gratitude.

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CHAPTER I

INTRODUCTION

In medicine and medical practice, the decision to use a drug for a particular disease is based on a multitude of factors. The main factor is that the drug needs to be both safe and effective for the target population and disease in which the drug is intended. If this drug is successful in the management of the disease, meets this main factor, and is in line with accepted clinical practice guidelines, it can be termed as the "standard of care" for that disease. Standard of care is defined as "guidelines that are generally accepted in the medical community for treatment of a disease or condition" and can be formally or informally introduced. [1] These guidelines can develop naturally over time as a disease is studied and the information is released, or they can develop through the stages of a clinical trial and their effectiveness proven through the rigorous nature of clinical trials. Even though this medical determination is deemed the standard of care, it can vary from doctor to doctor and community to community depending on the severity and nature of the disease.[2]

For chronic kidney disease (CKD), the National Kidney Foundation determined the guidelines to establish an effective standard of care to treat this serious and all too common condition. These guidelines include progression of kidney failure, decreased kidney function complications, the development of comorbid conditions especially cardiovascular disease, and the treatment to either slow progression or prevent disease development based on risk factors. As kidney failure progresses, complications can occur throughout the entire body, making treatment

of an already complicated and difficult disease even more cumbersome. In terms of treatment, dosing adjustments should be made based on the level of kidney function which can be determined by the glomerular filtration rate (GFR) and the associated anemia developed during the progression of the disease.[3] Currently, the standard of care for chronic kidney disease and its associated anemia is an injectable erythropoiesis-stimulating agent (ESA) that is given to patients that are dialysis-dependent and those that are not. This drug is useful in both instances as long as the hemoglobin (Hb) levels justify its administration and the benefits outweigh the risks. [4] In some cases, the standard of care can lag behind the best practices associated with a particular disease, and when it becomes apparent that this slow progression is happening or that other drugs, whether already approved or under investigation, could better fit the treatment of a particular disease, the need for a change in standard of care should be evaluated. [5]

As the standard of care is looking to be shifted in the treatment of CKD, the route of administration and the efficacy of the new treatment is also being scrutinized. A new treatment option currently under investigation is an oral hypoxia inducible factor prolyl-hydroxylase (HIF-PH) inhibitor that allows for titration of dosing—similar to that of the injectable formulation and promises to exhibit similar efficacy with lower side effects. The emphasis on side effects is important because the current treatment methods have been shown to increase cardiovascular events and the risk of stroke and death. [6] This investigational drug is being studied through a multi-site, international phase III clinical trial, and the data presented in this practicum is a portion of the data collected at this particular site during the duration of this trial.

Since the beginning of this trial, 26 subjects were successfully enrolled, 18 completed the first 52 weeks of the study, and 8 passed away before the 52-week mark. With such a small sample size, there is an emphasis on complete and accurate data collection, and the influence it

can have over the outcome of a site's statistics. Taking into account the small sample size, it is important to note that, although this data is useful, it does not represent the trial data as a whole. This data is used to show the trial outcome of this particular site and the efficacy and safety of these two medications in this group of subjects. This trial took place in Greenville, Texas, and being a more rural town compared to its larger, surrounding counterparts, this trial also shows the importance of having medication available outside of a doctor's office or dialysis clinic, pointing to the need for a more convenient medication.

CHAPTER II

BACKGROUND

Chronic kidney disease (CKD) is a common condition in the United States, affecting more than 30 million adults. It is termed chronic because it is damage that occurs to the kidneys over a long period of time—estimated three or more months. CKD over time can lead to end-stage renal disease (ESRD) which is kidney failure that is total and permanent and is treated with a kidney transplant or dialysis which is used to filter wastes and water from the blood artificially. The two types of dialysis are hemodialysis and peritoneal dialysis.[7] Hemodialysis is when filtering occurs outside of the body in a dialyzer and helps maintain mineral balance and control blood pressure. Peritoneal dialysis uses the peritoneum of the abdomen to filter the blood using a cleaning solution called dialysate. [8, 9] These two types of dialysis replace the loss of the glomerular filtration rate (GFR) which is how healthy kidneys filter waste and excess fluid.

The GFR helps outline CKD and is defined as a decrease of less than 60 mL/min/1.73 m^2. CKD is classified into five stages and termed G1 – G5. G1 is defined as kidney damage with normal or increased GFR greater than 90 mL/min/1.73 m^2 and is the only stage that uses an increased GFR as a method of diagnosis for kidney disease. Kidney damage with a mild decrease in GFR (60 – 89 mL/min/1.73 m^2) and persistent proteinuria defines G2. G3 and G4 are based on a moderate decrease (30 – 59 mL/min/1.73 m^2) and a severe decrease (15 – 29 mL/min/1.73 m^2) in GFR, respectively. G5 is termed kidney failure and occurs when a patient has a GFR of less than 15 mL/min/1.73 m^2 or is on dialysis.[10] These complex classifications are further detailed in

Table 1. GFR, a component of excretory function, is useful for classifying these stages of CKD because GFR and kidney function are directly related meaning that when GFR is reduced, there is widespread kidney damage and reduction in kidney function.[11] This damage and reduction is usually caused by the risk factors and comorbidities associated with CKD.

Table 1: CKD Stages and Classification

Stage	GFR (mL/min/m^2)	Indications/Symptoms
1	Normal or High > 90	Asymptomatic, increased creatinine or urea in the blood, blood or protein in the urine, evidence of kidney damage, history of Polycystic Kidney Disease (PKD), comorbidity of hypertension or diabetes
2	Mild 60 – 89	Asymptomatic, increased creatinine or urea in the blood, blood or protein in the urine, evidence of kidney damage, history of Polycystic Kidney Disease (PKD), comorbidity of hypertension or diabetes
3	Moderate 30 - 59	Development of uremia/anemia/bone loss, fatigue, edema, shortness of breath, passage of dark urine, kidney pain, trouble sleeping
4	Severe 15 - 29	Development of uremia/anemia/bone loss, fatigue, edema, shortness of breath, passage of dark urine, kidney pain, trouble sleeping, nausea/vomiting, metallic taste, urea breath, loss of appetite, difficulty concentrating, nerve problems
5	**End-Stage** **<15**	**Loss of appetite, nausea/vomiting, headaches, fatigue, difficulty concentrating, itching, no urine production, edema, cramps, nerve problems/tingling sensations, skin color changes, hypertension, anemia**

Cardiovascular disease is one major risk factor for CKD because it affects the structure and vasculature of the kidneys. Cardiovascular disease is present in 80 – 85% of CKD patients and is inversely proportional to GFR; as hypertension prevalence and vascular damage increases, GFR decreases. Hypertension is the prime cardiovascular event that causes the most issues in patients with CKD. Since the renal tissue and system is damaged, changes in blood pressure cannot be managed. As blood pressure increases, the kidneys are unable to activate and regulate the hormonal systems necessary to lower it, and a cycle of continuous damage occurs. Due to this cycle, more than half the deaths associated with CKD are contributed by onset or worsening of cardiovascular disease due to the release of proinflammatory cytokines that contribute to widespread damage.[12]

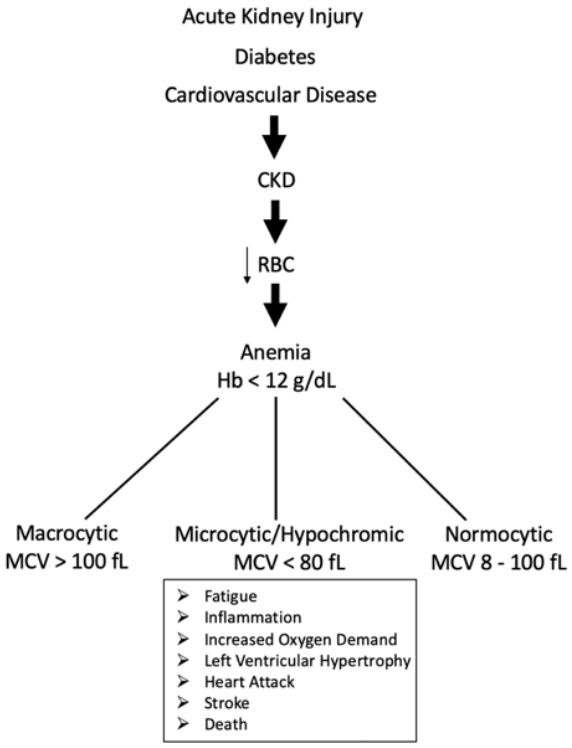
The other common risk factor for CKD is diabetes. Type II diabetes is the leading cause for diabetic related CKD although Type I diabetes for 5 or more years can also lead to the disease. The effects of diabetes on the kidneys is of a slower progression than cardiovascular disease, but damage can be detected through protein in the urine, high A1c, or blood glucose levels. One in four people with diabetes have CKD caused by high blood glucose levels, and this increased blood sugar results in vascular damage.[13, 14]

The vasculature, especially the microvasculature, of the kidneys is important for regulating blood flow and managing protein and fluid distribution and reabsorption. Altered filtration leads to waste and uric acid accumulation, altered electrolyte and mineral balance, decrease in urine production, and proteinuria. As this vasculature is damaged, fluid buildup occurs which puts unnecessary pressure on the kidney structures, leading to further damage.[15] Damage to the structure of the kidneys leads to destruction of the erythropoietin (EPO) centers within the cortex of the kidney located near the proximal convoluted tubule and the peritubular capillaries. These centers are important for making the EPO hormone which is sensitive to low oxygen levels and stimulates the bone marrow to make more red blood cells.[16] Stimulation of the bone marrow is important during these situations because low red blood cells and oxygen levels lead to anemia and subsequent cardiovascular incidences.

Anemia is common among patients with CKD, with its occurrence happening early in disease development and worsening as kidney function declines. [17] Anemia is a condition that results from having fewer red blood cells and consequently less oxygen carried to the tissues and organs. With this decline in oxygen availability, important organs such as the kidneys, heart, and brain cannot function efficiently. Unlike primary anemia that can be treated with oral iron or intravenous infusions and occurs due to continuous malabsorption in the gastrointestinal tract,

this anemia secondary to CKD occurs due to the destruction of the kidney structure and vasculature, which makes it harder to treat as more than stimulation of production of RBCs and iron absorption are needed. For this anemia, the EPO centers of the kidneys have to be stimulated or even artificially created through medication to placate this anemia. [18] Anemia that is secondary to CKD is attributed to the decline in EPO production and reduced GFR and occurs in over 90% of patients undergoing some sort of treatment for CKD. Along with reduction in EPO production, there has been evidence that a downregulation in hypoxia inducible factors (HIFs) are also responsible for the onset of anemia. Although EPO reduction is a sign of anemia, there is no level that can be deemed inadequate when distinguishing renal anemia from other forms of anemia. Measuring Hb levels is the current practice for determining anemia secondary to CKD. Anemia secondary to CKD is associated with increased cardiovascular incidence including inflammation, increased oxygen demand, left ventricular hypertrophy, myocardial infarction, and heart failure. Fatigue, depression, intolerance, stroke, and decreased quality of life also occur with anemia. Anemia, by itself, is associated with an increased risk of death and when associated with CKD, it is considered a mortality multiplier and magnifies this risk of death. Figure 1 outlines the progression of CKD and anemia to its associated outcomes. Due to these associated negative outcomes, a treatment for anemia secondary to CKD is necessary.[19]

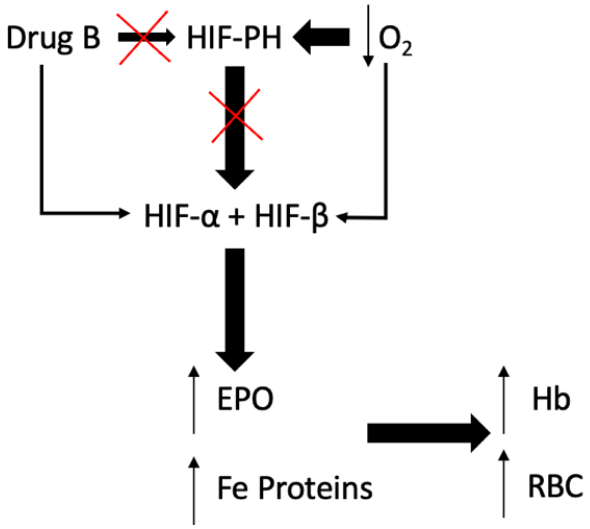
Figure 1: CKD and Anemia Flowchart



The standard method of treatment for this type of anemia is recombinant human erythropoietin (EPO), collectively called erythropoiesis-stimulating agents (ESAs). ESAs, although effective at managing anemia and increasing erythropoiesis, fail to reach target Hb levels and increase the risk of cardiovascular events and AEs with increased doses. It is these increased doses and relative resistance that can occur in some patients that increases these risks, especially the cardiovascular risk, as ESAs tend to have off-target effects on cardiac and other tissues. The standard ESA being prescribed is an injection that stimulates the bone marrow to make more red blood cells and has a prolonged half-life which allows for dosing schedules to be further apart than other ESAs. With a prolonged half-life, its effects can be observed longer, but the risk of accumulation is high. Since this drug can increase the amount of red blood cells produced, there is a risk that increasing EPO can deplete iron pools and further exacerbate the state of anemia.[20,21]

The novel and alternative drug being studied is an oral tablet that is a hypoxia inducible factor prolyl-hydroxylase (HIF-PHs) inhibitor designed to mimic the body's response to low blood oxygen. Through HIF-PH inhibition, this drug stabilizes alpha HIFs and stimulates the production of EPO from renal sites, resulting in an increase in RBC production in the bone marrow[22]. This mechanism of action is outlined in Figure 2. An increase in EPO allows for iron homeostasis which enhances the terminal steps of erythropoiesis. This oral medication also has dual routes of elimination and, therefore, the risk of accumulation in patients with CKD is reduced. Even with the positive outlooks associated with this medication, there is still a cardiovascular risk shown in phase I and II trials to be increased palpitations and incidence of coronary artery disease.[23, 24]

Figure 2: Drug B (HIF-PH Inhibitor) Mechanism of Action



Aside from the mechanism of action of these two drugs, the routes of administration are also important factors. Routes of administration greatly affect the bioavailability of a drug due to the biologic and metabolic barriers the drug may have to cross in order to work effectively and remain within its therapeutic window. Drug administration can be divided into two main

categories, parenteral and enteral administration. Parenteral administration bypasses the gastrointestinal tract and is preferred when a drug has low oral bioavailability, its effects are needed immediately, or its rate of duration or absorption needs to be closely controlled or monitored. These routes include intramuscular, subcutaneous, transdermal, inhalational, intrathecal, and intravenous. With an intravenous route, the administration is precise and allows for therapeutic concentrations to be achieved rapidly. The bioavailability of this route is 100% since it is delivered into the vascular space. Although this route has many benefits, there is also a risk of embolism, overdose, and other adverse effects, such as the formation of precipitates, if given incorrectly. Enteral administration, such as oral, rectal, or sublingual, allows for partial absorption of the drug within the gastrointestinal tract before it reaches its target, which is termed the first-pass effect. This route is useful when a drug has a high oral bioavailability and are acid stable. With an oral route, the administration is more convenient, affordable, and easier to take, but due to the first-pass effect, its overall absorption is variable for each patient. Also, with this route, patient compliance varies greatly. [25, 26] Although there is not a study specifically tailored to evaluate the difference in administration of these two drugs, there is a trial that is looking into their effectiveness long term.

The current study to compare the standard of treatment and the investigational drug is a phase III interventional, international, randomized, parallel, and open label clinical trial. This study targeted to enroll approximately 2200 subjects at 300 investigative sites across North America, Latin America, Europe, and Asia Pacific. This trial is looking to establish efficacy and safety of the oral alternative and determine the AEs of the drug when compared to the standard of care. The primary outcomes of this study are to evaluate the mean change in Hb from baseline and determine the major adverse cardiovascular events. [27] During phase I trials, the oral tablet

was well tolerated in healthy individuals and increased plasma EPO and Hb levels. Phase II studies showed that in the target population, the oral alternative had limited fluctuations in Hb levels and improved iron absorption.[28] With the success of the phase I and II trials, phase III is looking to replicate these results while expanding the knowledge and effects of this drug. In order for the outcomes of this phase III trial to warrant the continuance of the oral alternative down the developmental pipeline, accurate data collection and analysis are important.

The success of clinical trials relies on the accuracy of the data collected. The data that is collected needs to be of high-quality, have limited number of errors and missing data points, and should be fit for statistical analysis. As data is collected, it should be reviewed for trends and outcomes that support the primary and secondary outcomes and provide a perspective that allows others to understand and appreciate the data presented. Along with these parameters, data should correlate with the end goals of the study and the protocol and comply with regulatory guidelines. The data points collected during a clinical trial are imperative to moving a drug through the developmental pipeline and to the appropriate consumers. [29] With these excellent data management practices in mind, the data collected and analyzed through this research practicum can be successfully used to determine the next phase that the oral alternative will progress to.

Significance

The need for a new method of therapy for anemia secondary to CKD is important for both patients and physicians. This type of anemia is difficult to treat because it is generally caused by more than just the CKD alone. Other factors influence the extent of the anemia including vitamin deficiencies, EPO suppression, and iron deficiency, and although the current standard is beneficial in managing the anemia and increasing EPO, increased dosage can cause more harm than good.

Considering that most patients with CKD have comorbidities, it is important that they have options to consider that are suitable for their quality of life. The current treatment for anemia in this population is an injection, and although it can be given during dialysis, most patients do not have dialysis treatments every day. When these patients are not in the clinic, the care giver or the patient is responsible for giving the injection in the correct manner whether that is intravenously or subcutaneously. Aside from the inconvenience of this method of treatment, the safety risks associated are a major concern. Injectable ESAs tend to carry a high risk of mortality and cardiovascular events especially when trying to reach higher Hb levels. Due to these associated risks, it is apparent that, as the unmet medical need for anemia management grows, the efficacy of a drug that can minimize or all together avoid these risks is necessary.

The type of drug, on the other hand, that could possibly meet this need and expectation, is an oral form of medication that can be taken every day. This method of treatment would be easier for the patient to comply with because no needles are involved which reduces the discomfort and the risks associated with repetitive injections. It would offer a more flexible dosing schedule and reliable titration method than an injection which is important when dealing with a value that should be kept in a certain range, which was 10 g/dL to 11 g/dL for this trial.

The titratable ease of this drug may help avoid the Hb overshoots that can occur and allow for a stable increase in Hb levels. It is important to reduce Hb overshoots, especially above 11 g/dL, as this increases the risk for RBC clot formation which would cause further damage to an already fragile vasculature.

With the ease of treatment that could become possible with the implementation of Drug B (HIF-PH inhibitor), the addition of other management outcomes could also help improve patient's quality of life. HemoCue® Devices could be implemented with patient's that are receiving in-home care or even those receiving in-clinic dialysis which would allow them to check their Hb levels often and communicate to their doctor their need for a dosing change in correlation with their symptoms. It would also decrease the amount of lab draws patients would have to receive and how often they would have to go to a kidney care center. Also, this oral alternative is taken daily which would help with the severe decreases in Hb values that are seen with the injection as these doses are spread out and decreases in Hb not detected until a dialysis treatment. This medication could allow for a safe and effective way to manage the patient's anemia while allowing them to take it with their other comorbid oral medications without adding a separate and undue burden to the patient.

CHAPTER III

PROBLEM AND HYPOTHESIS

CKD affects 1 in 10 adults or approximately 14% of the general population in the United States. It is a serious illness that is generally preceded by diabetes and hypertension. Both comorbid conditions can lead to the slow and steady deterioration of kidney function and destruction of nephron microvasculature. This disease can be silent in some patients and may not be diagnosed until a later stage due to its gradual and insidious development. Early diagnosis and treatment are crucial in order to avoid irreparable damage to the kidney and other organ systems such as the heart. As CKD develops, the structure and vasculature of the kidneys are damaged which leads to the need for dialysis due to altered electrolyte absorption/excretion and waste product accumulation; it also leads to secondary conditions such as heart disease and anemia. [30] Anemia is particularly present in patients with end-stage 3 or 4 CKD, and this comorbidity is prevalent in over 50% of patients with CKD. This anemia develops due to the destruction of the erythropoietin (EPO) centers in the kidney. Without EPO, the bone marrow receives a lack of signaling and can no longer efficiently produce red blood cells, exacerbating the anemia and causing the need for ESA treatment.[31]

The current method of treatment for DD-CKD is an injectable medication termed Drug A (ESA). It is usually given intravenously or subcutaneously at home, in the doctor's office, or directly into the dialysis access or fistula. The issue with this drug is that it has not been shown to improve the effects of anemia—tiredness, fatigue, and poor well-being—and has an increased

risk of hypertension.[32] Considering that high blood pressure is a risk factor for CKD, this is a major concern and the reason another treatment method is being investigated. Drug B (HIF-PH inhibitor) is the oral alternative being investigated and has been shown, in phase I and II trials, to increase EPO and Hb from baseline, respectively[18]. Since this drug is investigational, an extensive list of side effects are not available, but the primary complaint amongst study subjects is nausea. [1]

For this research practicum, I hypothesize that Drug B (HIF-PH inhibitor) will help better manage anemia secondary to CKD with better outcomes in increasing and maintaining Hb levels and has fewer adverse events when compared to the injection. A better route of administration and efficacy of Drug B (HIF-PH inhibitor) will give CKD patients and their physicians a superior alternative to ESAs and anemia treatment.

Hypothesis: Drug B (Hypoxia Inducible Factor Prolyl-Hydroxylase (HIF-PH) Inhibitor) helps better manage anemia secondary to CKD with fewer adverse events when compared to the standard of care.

Aim 1: Assess the efficacy of Drug B (HIF-PH inhibitor) in comparison with the standard of care from baseline.

Aim 2: Determine the effect that Drug B (HIF-PH inhibitor) has on CKD with secondary anemia and the AEs of this treatment in regard to these subjects.

CHAPTER IV

METHODS AND STATISTICAL ANALYSIS

This retrospective analysis is over a 52-week study with each subject starting at different time points over the 1-year period. Subjects were enrolled based on the inclusion and exclusion criteria that was determined by the sponsor. From baseline, subjects were randomized into two study arms for open-label evaluation of each treatment: Drug A (ESA) which is the injection and Drug B (HIF-PH inhibitor) which is the oral tablet. During the time the subjects were enrolled in the study, Hb levels were evaluated at different time points based on the study timeline. Within the 52-weeks, known as the "Efficacy Periods" of the study, there were four evaluation periods. Establishment of dosage and acclimation of medication was evaluated at weeks 0-9, primary efficacy was evaluated at weeks 10-16, and secondary efficacy was evaluated at weeks 32-40. End of treatment was evaluated as a comparison to baseline and the establishment period. The efficacy points are further described in Table 2.

Table 2: Study Efficacy Periods Overview

	Hb Maintenance	Primary Efficacy Point	Secondary Efficacy Point	End of Treatment
Week	0 - 9	10 - 16	32 - 40	52
Visits	1 - 5	6 - 8	12 - 14	17
Overview	Establishment of dosage	Change from Treatment Period 1 to Treatment Period 2	Midpoint of Treatment Period 2	Study Endpoint

For measurement of Hb levels, blood draws were done and HemoCue® point of care device was used. To qualify for enrollment and randomization, subject's initial Hb values had to be between 8.0 g/dL and 11.0 g/dL. Hb levels were measured every 2 weeks during "treatment

period 1" which was weeks 0 – 12 (Visits 1 – 7) and every 4 weeks unless otherwise specified during "treatment period 2" which was weeks 13 – 52 (Visits 8 – 17). Table 3 illustrates the study timeline with the corresponding visits to weeks. These levels were then compared, after randomization, to the necessary Hb range, between 10.0 g/dL and 11.0 g/dL, to determine dosing changes for both study arms. Although complete blood count (CBC) were also performed through these blood draws to evaluate efficacy and safety, only HemoCue® values were used to assess dosing changes.

Table 3: Study Timeline

Study Term	***Study Visit***	***Corresponding Week***
Treatment Period 1	*1*	*0*
	2	*2*
	3	*4*
	4	*6*
	5	*8*
	6	*10*
	7	*12*
Treatment Period 2	*8*	*16*
	9	*20*
	10	*24*
	11	*28*
	12	*32*
	13	*36*
	14	*40*
	15	*44*
	16	*48*
	17	*52*

Dosing for both arms was either increased (under 10 g/dL), decreased (above 11 g/dL), or unchanged (within range) based on the obtained Hb values. Initial dosing for Drug A (ESA) was determined by the prior dosing regimen of the subject if previously prescribed with the medication or based on the approved product label. Drug A (ESA) was administered intravenously depending on the prescribed dosing schedule which follows the local standard of

care and was independent of the visit schedule. Dosing adjustments for this arm of the study were guided by the sponsor's dosing portal and investigator discretion. Initial dosing for Drug B (HIF-PH inhibitor) was 300 mg once a day and taken at roughly the same time every day. Dosing adjustments were determined by Hb concentrations and a dose adjustment algorithm by the sponsor. Dosing regimens were changed by one tablet (150 mg) increments and reviewed by the investigator. If levels fell below 10.0 g/dL, dosing was increased by 150 mg and if levels increased above 11.0 g/dL, dosing was interrupted and then decreased by the same amount until levels fell within the specified range. The dosing adjustments for Drug B (HIF-PH inhibitor) are outlined in Table 4. For Drug B (HIF-PH inhibitor), frequent dosing adjustments should have been minimized; meaning that an increase in dose should not occur more than once every 4 weeks but decreases in doses could have occurred more often.

Table 4: Dosing Adjustments for Drug B (HIF-PH Inhibitor)

Hb Values (g/dL)	Dosing Change
Low < 9	↑ Dose by 150 mg
Normal 10 – 11	Maintain Current Dose
Moderate > 11	↓ Dose by 150 mg
High > 12	Interrupt Current Dose

The other variables other than the Hb values and dosing that were evaluated over the 52 weeks for this analysis were iron supplementation, ESA rescues, RBC transfusions, and AEs. Iron was given during this study to maintain ferritin concentrations. ESA rescues were used when subject's symptoms of anemia were severe or the Hb levels fell below 9.0 g/dL. In cases where acute or severe blood loss occurred, worsening of anemia, or moderate to severe symptoms of anemia, RBC transfusions were used. AEs were recorded based on type and severity.

The major variables that were compared were Hb values between the two study arms (measured in g/dL), AEs based on classification and severity, and supplementations and rescues. Hb values were evaluated for each study arm as a whole and subcategorized based on the study timeline. These values were broken down based on baseline, weeks 10 – 16, weeks 32 – 40, and week 52 values. Efficacy Period values were also analyzed based on the three periods evaluated during this time.

Statistical Analysis

The primary outcome variables were analyzed using descriptive statistics and contingency tables. Mean Hb response for both drugs were calculated using a pivot table to evaluate mean Hb response at each dose level. Comparison of Hb ranges for each drug were analyzed using a Fisher's Exact Test due to the small sample size. Additionally, Hb response to Drug A and B were tested for significance using an unpaired t-test assuming unequal variances. Variance was determined through an F-Test.

The secondary outcomes were analyzed through descriptive statistics as well. Chi-Square tests were used to determine independence between the secondary outcomes of the 2 drugs. The secondary outcomes were further analyzed for significance using Fisher's Exact Test.

Accuracy of data collection was evaluated at the end of data analysis to emphasize the importance of correct data recording and reporting. Analysis was performed in RStudio with a 95% confidence level and a p-value of 0.05 for T-Tests and 0.01 for Fisher's Exact Test.

CHAPTER V

RESULTS

Drug A (ESA) and Drug B (HIF-PH Inhibitor) Hb Responses and Efficacy Timepoints

In this study, retrospective data obtained from a total of 18 subjects were used to analyze the specified timepoints between Baseline (Wk 0) and End of Treatment (Wk 52). There were a total of 17 visits and 2 efficacy timepoints. Out of the 18 subjects, 10 were randomly assigned to Drug A (ESA) and 8 randomly assigned to Drug B (HIF-PH inhibitor). The timeline was broken down into Baseline (Wk 0), Efficacy Period 1 (Wk 10 – 16), Mid-Efficacy (Wk 20 – 28), Efficacy Period 2 (Wk 32 – 40), and Ending Period (Wk 44 – 52). This timeline corresponded with the end of the treatment period 2 of the study. The Hb values for each drug and period were analyzed based on the mean, median, and range of the values.

The Drug A (ESA) mean Hb for Baseline was 9.93 $\pm$ 1.238 g/dL, Efficacy Period 1 was 10.21 $\pm$ 0.814 g/dL, Mid-Efficacy was 9.87 $\pm$ 0.964 g/dL, Efficacy Period 2 was 10.41 $\pm$ 1.181 g/dL, Ending Period was 10.25 $\pm$ 1.044 g/dL, and Total was 10.14 $\pm$ 0.389 g/dL. The Drug B (HIF-PH inhibitor) mean Hb for Baseline was 9.45 $\pm$ 1.826 g/dL, Efficacy Period 1 was 10.14 $\pm$ 1.211 g/dL, Mid-Efficacy was 9.53 $\pm$ 1.151 g/dL, Efficacy Period 2 was 10.19 $\pm$ 1.131 g/dL, Ending Period was 9.49 $\pm$ 1.601 g/dL, and Total was 9.69 $\pm$ 0.654 g/dL. Dosing frequencies were analyzed using the same methods, whereas dosing changes were summarized as counts and percentages. For Drug B (HIF-PH inhibitor), compliance was calculated to determine the overall compliance score for the 8 subjects over the 52-weeks.

This data shows that the mean Hb levels during the different periods vary as there is an increase in mean Hb in both drugs during the 2 efficacy periods when compared to baseline, mid-efficacy, and end of treatment suggesting that there are optimal periods in which each drug is effective. This fluctuation in Hb levels was not previously seen in the Phase I or Phase II trials for Drug B (HIF-PH inhibitor). Tables 5 and 6 display this information.

Table 5: Complete Primary Outcomes—Drug A (ESA)

Drug A Total Values	**Baseline (Wk 0)**	**Efficacy 1 (Wk 10 – 16)**	**Mid-Efficacy (Wk 20 – 28)**	**Efficacy 2 (Wk 32 – 40)**	**Ending Period (Wk 44 – 52)**	**End of Treatment (Wk 52)**	**Total Values Baseline – Wk 52**
Hb Values (g/dL)							
Mean ± Stdev	9.93 ± 1.238	10.21 ± 0.814	9.87 ± 0.964	10.41 ± 1.181	10.25 ± 1.044	9.84 ± 0.956	10.14 ± 0.389
Median	10.15 (S1 – S10)	10.20 (S1 – S10)	10.05 (S1 – S10)	10.50 (S1 – S10)	10.40 (S1 – S10)	9.75 (S1 – S10)	10.14 (Wk 1 – Wk 52)
Range	3.9 (11.5 – 7.6)	3.9 (12.3 – 8.4)	4.6 (12.1 – 7.5)	6.2 (12.8 – 6.6)	3.7 (12.0 – 8.3)	3.3 (11.7 – 8.4)	1.3 (10.9 – 9.6)
Dosing Frequency mcg/kg QW							
Mean ± Stdev	30.00 ± 13.33	27.75 ± 27.91	30.33 ± 25.43	27.58 ± 26.91	25.22 ± 26.14	22.78 ± 22.60	27.45 ± 18.93
Median	30 (S1 – S10)	20 (S1 – S10)	25 (S1 – S10)	22.5 (S1 – S10)	20 (S1 – S10)	22.5 (S1 – S10)	22.79 (Wk 1 – Wk 52)
Range	40 (50 – 10)	100 (100 – 0)	100 (100 – 0)	100 (100 – 0)	100 (100 – 0)	80 (80 – 0)	68.5 (83.5 – 15)
Dosing Changes (Count)							
Maintenance Dose	20	14	14	15	9	3	72
Increased Dose	10	10	12	4	13	5	49
Decreased Dose	3	0	1	6	2	0	12
Interrupted Dose	7	6	3	5	6	2	27
Total Doses	40	30	30	30	30	10	160
Total Dosing Changes	19	14	13	16	20	N/A	82

Table 6: Complete Primary Outcomes—Drug B (HIF-PH Inhibitor)

Drug B Total Values	**Baseline (Wk 0)**	**Efficacy 1 (Wk 10 – 16)**	**Mid-Efficacy (Wk 20 – 28)**	**Efficacy 2 (Wk 32 – 40)**	**Ending Period (Wk 44 – 52)**	**End of Treatment (Wk 52)**	**Total Values Baseline – Wk 52**
Hb Values (g/dL)							
Mean ± Stdev Median Range	9.45 ± 1.826 9.8 (S1 – S10) 5.5 (12.1 – 6.6)	10.14 ± 1.211 10.25 (S1 – S10) 4.7 (12.5 – 7.8)	9.53 ± 1.151 9.60 (S1 – S10) 4.3 (11.4 – 7.1)	10.19 ± 1.131 10.25 (S1 – S10) 4.5 (12.3 – 7.8)	9.49 ± 1.601 9.30 (S1 – S10) 6.0 (12.7 – 6.7)	10.54 ± 1.919 10.65 (S1 – S10) 5.3 (12.7 – 7.4)	9.69 ± 0.654 9.78 (Wk 1 – Wk 52) 1.9 (10.9 – 9.0)
Dosing Frequency mcg/kg QD							
Mean ± Stdev Median Range	300.00 ± 0.00 300 (S1 – S10) 300 (300 – 0)	212.50 ± 202.30 150 (S1 – S10) 600 (600 – 0)	331.25 ± 242.19 450 (S1 – S10) 600 (600 – 0)	287.50 ± 257.60 450 (S1 – S10) 600 (600 – 0)	231.25 ± 268.98 0 (S1 – S10) 600 (600 – 0)	262.50 ± 297.31 150 (S1 – S10) 600 (600 – 0)	256.99 ± 132.68 309 (Wk 1 – Wk 52) 335 (370 – 53)
Dosing Changes (Count)							
Maintenance Dose	13	10	10	11	6	1	50
Increased Dose	7	5	7	3	5	3	27
Decreased Dose	3	1	0	0	0	0	4
Interrupted Dose	9	8	7	10	13	4	47
Total Doses	32	24	24	24	24	8	128
Total Dosing Changes	13	9	7	5	7	N/A	41
Compliance %	90.652	89.737	90.722	89.000	98.278	97.333	89.924

When comparing the main primary endpoint of the study, Baseline Hb (Wk 0) was compared to End of Treatment (Wk 52) to determine if there was a significant difference between the 2 time periods. An F-test was performed to determine Hb variance between the 2 drugs. It was determined that the variances (1.02 for Drug A (ESA) and 1.94 for Drug B (HIF-PH inhibitor)) were not equal and allowed for the use of a two-sample t-test assuming unequal variances. There was a significant difference between the Hb levels for Drug A (ESA) compared to Drug B (HIF-PH inhibitor) from Baseline to Week 52 ($p = 0.002$) and the null hypothesis of equal means is rejected. When all Hb values were compared for the total length of the retrospective analysis for each drug using the same test, there was not a significant difference between Baseline and Total Hb values over the entire 52 weeks.

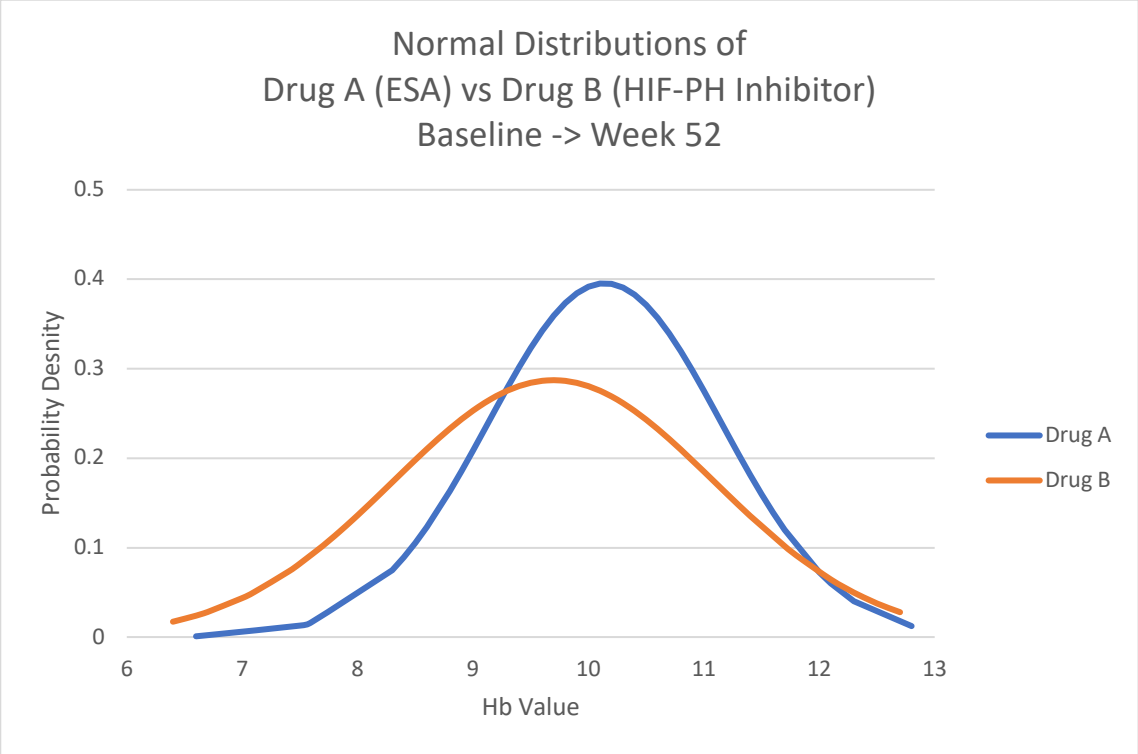
Graphing the normalized Hb values resulted in two bell-shaped curves with different distributions. For Drug A (ESA), the distribution of Hb was taller and narrower than Drug B (HIF-PH inhibitor) whose distribution was wider and more spread out during the 52 weeks. This graph suggests that Drug A (ESA) may be better at maintaining stable Hb levels than Drug B (HIF-PH inhibitor). Even though there is a statistically significant difference between the 2 drugs, the clinical significance cannot be determined based on the small sample size and short timeline. Table 7 and Figure 3 further detail this information.

Table 7: Primary Endpoint—Drug A (ESA) and Drug B (HIF-PH Inhibitor) Hb from Baseline to Week 52

Numerical Values	**Baseline (Wk 0)**	**End of Treatment (Wk 52)**	**p-Value**
Drug A Hb Values (g/dL)			
Mean ± Stdev	9.93 ± 1.238	9.84 ± 0.956	0.00215696*
Median	10.15 (S1 – S10)	9.75 (S1 – S10)	
Range	3.9 (11.5 – 7.6)	3.3 (11.7 – 8.4)	
Drug B Hb Values (g/dL)			
Mean ± Stdev	9.45 ± 1.826	10.54 ± 1.919	
Median	9.8 (S1 – S10)	10.65 (S1 – S10)	
Range	5.5 (12.1 – 6.6)	5.3 (12.7 – 7.4)	

*Two-Sample T-Test Assuming Unequal Variances (two-tailed test) showed a significant difference between Baseline and End of Treatment after determination of mean and variance.

Figure 3: Normal Distribution of Hb from Baseline to Week 52



When further breaking down the timeline into its perspective periods, efficacy periods were categorized into the following: Baseline (Wk 0) to Efficacy Period 1 (Wk 10 -16), Efficacy Period 1 (Wk 10 – 16), Efficacy Period 1 (Wk 10 – 16) to Efficacy Period 2 (Wk 32 – 40), Efficacy Period 2 (Wk 32 - 40), and Efficacy Period 2 (Wk 32 – 40) to End of Treatment (Wk 52). The timepoints in-between the efficacy periods, labeled Mid-Efficacy (Wk 20 – 28) and Ending Period (Wk 44 – 52), were used in this analysis. The same F-test to determine variance and subsequent t-test were used to establish significance between these periods. From Baseline (Wk 0) to Efficacy Period 1 (Wk 10 -16), there was a significant difference in Hb levels ($p = 0.046$) meaning that during this period, there was a significant increase in the Hb levels of those subjects using Drug B (HIF-PH inhibitor) than those using Drug A (ESA). For the other periods, Efficacy Period 1 (Wk 10 – 16), Efficacy Period 1 (Wk 10 – 16) to Efficacy Period 2 (Wk 32 – 40), Efficacy Period 2 (Wk 32 - 40), and Efficacy Period 2 (Wk 32 – 40) to End of Treatment (Wk 52), there was no statistical significance between the Hb levels with p-values > 0.05. Graphically showing the information for Efficacy Period 1 shows that for both drugs, the Hb values are concentrated around the same values for Efficacy Period 1, but that Drug B (HIF-PH inhibitor) has a slightly wider distribution than Drug A (ESA). For Efficacy Period 2, the graph shows that both drugs have relatively the same distribution and Hb concentration. These graphs further represent that the difference between the 2 periods were not statistically different. Table 8 and Figure 4 and 5 further detail this information.

Table 8: Primary Endpoint—Drug A (ESA) and Drug B (HIF-PH Inhibitor) Hb of Efficacy Period 1 and 2

Numerical Values	**Baseline (Wk 0)**	**Efficacy 1 (Wk 10 – 16)**	**Mid-Efficacy (Wk 20 – 28)**	**Efficacy 2 (Wk 32 – 40)**	**Ending Period (Wk 44 – 52)**	**End of Treatment (Wk 52)**	**p-Value**
Drug A Hb Values (g/dL)							
Mean ± Stdev	9.93 ± 1.238	10.21 ± 0.814	9.87 ± 0.964	10.41 ± 1.181	10.25 ± 1.044	9.84 ± 0.956	
Median	10.15 (S1 – S10)	10.20 (S1 – S10)	10.05 (S1 – S10)	10.50 (S1 – S10)	10.40 (S1 – S10)	9.75 (S1 – S10)	
Range	3.9 (11.5 – 7.6)	3.9 (12.3 – 8.4)	4.6 (12.1 – 7.5)	6.2 (12.8 – 6.6)	3.7 (12.0 – 8.3)	3.3 (11.7 – 8.4)	0.04628813*
Drug B Hb Values (g/dL)							
Mean ± Stdev	9.45 ± 1.826	10.14 ± 1.211	9.53 ± 1.151	10.19 ± 1.131	9.49 ± 1.601	10.54 ± 1.919	
Median	9.8 (S1 – S10)	10.25 (S1 – S10)	9.60 (S1 – S10)	10.25 (S1 – S10)	9.30 (S1 – S10)	10.65 (S1 – S10)	
Range	5.5 (12.1 – 6.6)	4.7 (12.5 – 7.8)	4.3 (11.4 – 7.1)	4.5 (12.3 – 7.8)	6.0 (12.7 – 6.7)	5.3 (12.7 – 7.4)	

*Two-Sample T-Test Assuming Unequal Variances (two-tailed test) showed a significant difference between treatment periods after determination of mean and variance.

Figure 4: Normal Distribution of Hb Efficacy Period 1

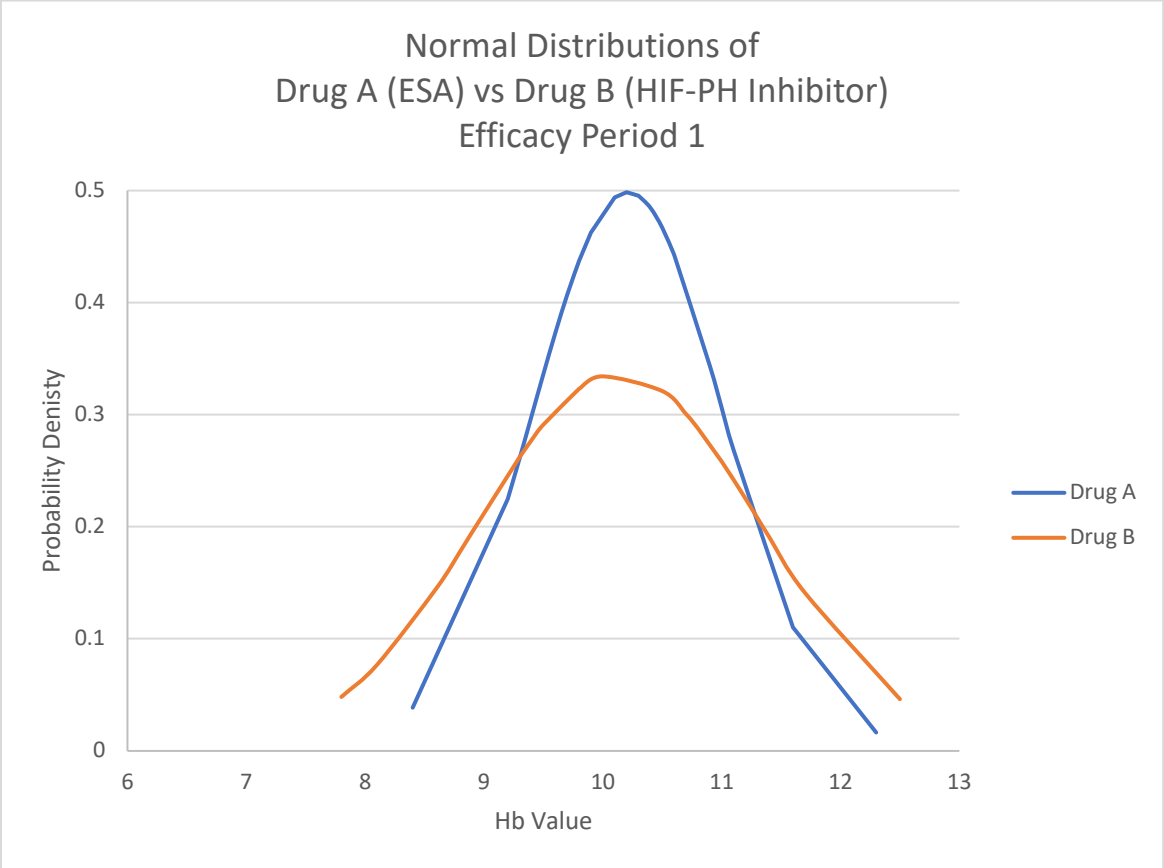
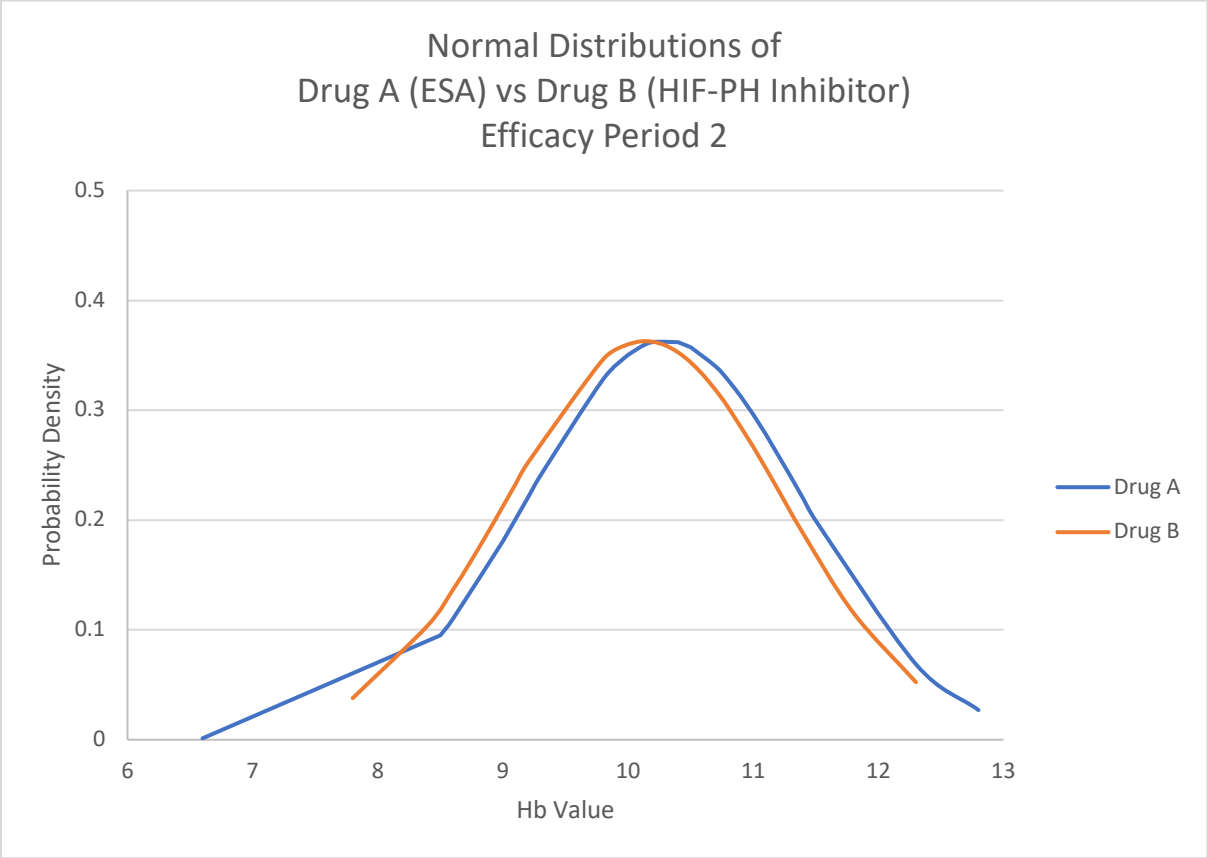


Figure 5: Normal Distribution of Hb Efficacy Period 2



When analyzing Hb ranges and dose response for both the drugs, the mean Hb in range, the dosing changes, and the mean Hb response were considered for analysis. A 2x2 table was constructed to compare the counts of mean Hb values between Drug A (ESA) and Drug B (HIF-PH inhibitor) that were either within an acceptable Hb range as indicated by the protocol or out the acceptable Hb range. There was a statistically significant difference between in-range and out-of-range Hb response to Drug A (ESA) and Drug B (HIF-PH inhibitor). (Baseline (Wk 0) and End of Treatment (Wk 52), $p = 0.0005$). An Odds Ratio (OR) was also calculated to determine the likelihood of the Hb being in range occurring. According to the data, Drug A (ESA) is 2.4 times more likely to have a Hb value in range than Drug B (HIF-PH inhibitor) suggesting a better management of the secondary anemia. With a p-value <0.01 and the confidence interval range being above 1.0, the null hypothesis that the probability of no difference in Hb range is rejected. A Chi-square test was also performed to evaluate whether the Hb range was independent from the drugs, which it is not. Both Drug A and B are not independent of the Hb range and have direct effects on the Hb levels.

For dosing changes, the total dosing changes were added and the mean calculated among the 2 drugs. The total doses for each drug were compared and found to be statistically insignificant based on the p-value and an OR of <1. When comparing the different dosing changes, 45% of Drug A (ESA) and 39.1 % of Drug B (HIF-PH inhibitor) were maintenance doses, 30.6% of Drug A (ESA) and 21.1% of Drug B (HIF-PH inhibitor) were increased doses, 7.5% of Drug A (ESA) and 3.1% of Drug B (HIF-PH inhibitor) were decreased doses, and 16.9% of Drug A (ESA) and 36.7% of Drug B (HIF-PH inhibitor) were interrupted doses. Drug A (ESA) had more maintenance doses than Drug B (HIF-PH inhibitor) meaning that a stable dose is perhaps more achievable with Drug A (ESA) despite there being more dosing changes to

establish that stable dose. Using a t-test. there was no significant difference between the maintenance doses, increased doses, and decreased doses. There was a significant difference between the interrupted doses where the drugs had to be stopped either due to high Hb levels, AEs, or supplementation. Even though there was a significant difference ($p = 0.004$) the OR was < 1 meaning that there was a decreased likelihood that fewer interrupted doses would occur due to Drug A (ESA). In addition to the dosing changes, the compliance score was also calculated. Drug A (ESA) had 100% compliance since those doses were given in office, whereas Drug B (HIF-PH inhibitor) had 89.92% compliance. Per study protocol, this is deemed as a good compliance score, showing that keeping a high compliance score is possible with the oral medication and implying that it may have an easier route of administration. Table 9 details the above information.

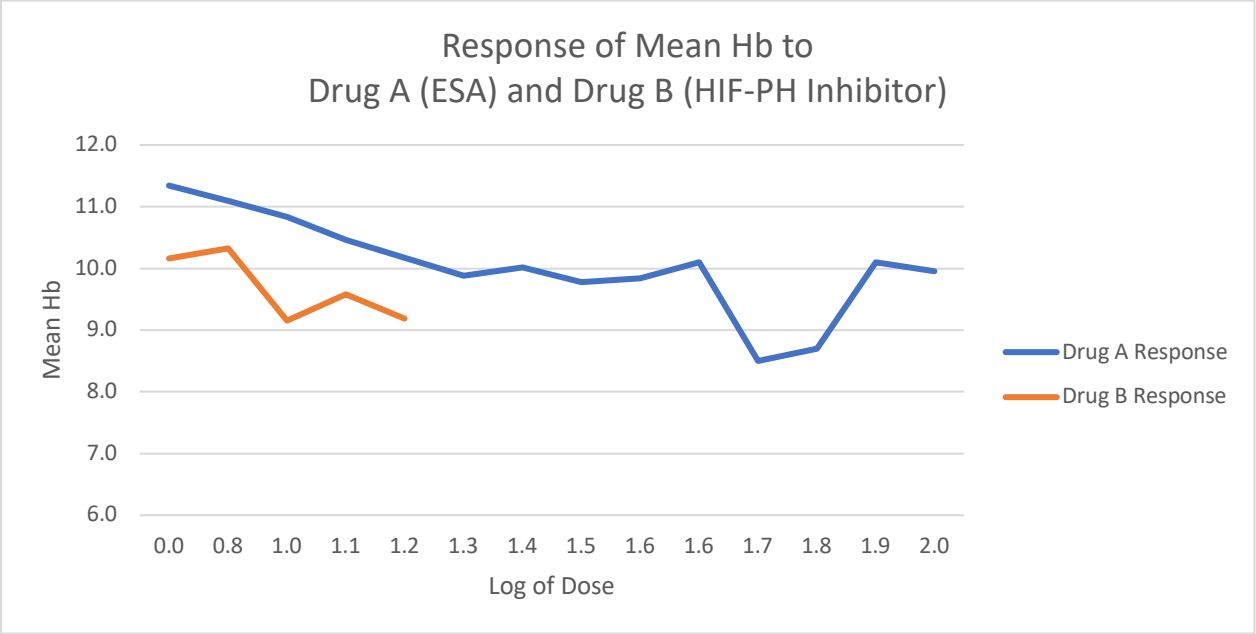
For evaluation of the mean Hb response to the drugs, a pivot table was used to calculate the mean Hb values for every dose level. The graph (Figure 6) shows that lower doses for both drugs may be more beneficial when keeping the Hb within the specified range which correlates with previous studies, but further evaluation of this data is necessary.

Table 9: Drug A (ESA) and Drug B (HIF-PH Inhibitor) Mean Hb Dose Response

Wk 52 (17 Visits) Hb Range: 10 – 11 g/dL	**Drug A**	**Drug B**	**p-Value**	**Odds Ratio (OR)**
Mean Hb in Range (% of the time)	44.7%	25.0%	0.0004703*	2.420453
Total Dosing Changes	82	41		
Mean Dosing Changes	8.1	5.1		
Total Doses	160	128	0.7618	0.8013681
Total Maintenance Doses	72	50	0.586	1.151602
Percentage	45%	39.1%		
Total Increased Doses	49	27	0.1924	1.450382
Percentage	30.6%	21.1%		
Total Decreased Doses	12	4	0.1941	2.393638
Percentage	7.5%	3.1%		
Total Interrupted Doses	27	47	0.004029*	0.4605648
Percentage	16.9%	36.7%		
Compliance Percentage (%)	100%*	89.92%		

*Fisher's Exact Test showed a significant difference between Drug A and B after test for independence and likelihood. An OR > 1 shows that the likelihood of an event is more likely to occur in Drug A than Drug B.

Figure 6: Mean Hb Response of Drug A (ESA) and Drug B (HIF-PH Inhibitor)



Drug A (ESA) and Drug B (HIF-PH Inhibitor) Secondary Endpoints

Evaluation of the secondary endpoints, using counts of occurrence, were analyzed and found to be statistically significant between Drug A and B for supplementation except for Blood Transfusions. For ESA Rescue ($p = 0.0005$), ESA Rescue with Drug A ($p = 0.0087$), and Iron Supplementation ($p = 0.0003$), there was a statistically significant difference in their occurrence. The OR for both ESA determinations were <1 indicating that there is not a stronger likelihood of occurrence in Drug A (ESA) than Drug B (HIF-PH inhibitor) in overall supplementation. ESA rescue for both groups were administered as needed and used when Hb levels were consistently < 9 g/dL and it was determined that additional Drug A (ESA) be given, or a different type of ESA administered to help raise the Hb level. For Blood Transfusions and Iron Supplementation, the OR > 1 indicates that Blood Transfusions are 6.5 times and Iron Supplementations are 3.2 times more likely to occur in Drug A (ESA) when supplementation is involved.

For Drug A (ESA), 10% of subjects needed some sort of ESA rescue, 10% needed Blood Transfusions, and 80% needed Iron Supplementation over the 52 weeks. Overall for Drug B (HIF-PH inhibitor), 87.5% of subjects needed some sort of ESA Rescue, 50% needed Blood Transfusions, and 100% needed Iron Supplementation over the 52 weeks. Since the amount of total supplementation between the 2 drugs varied greatly, clinical significance cannot be accurately determined. Table 10 summarizes this dataset.

Table 10: Drug A (ESA) and Drug B (HIF-PH Inhibitor) ESA Rescue and Supplementation

Wk 52 (17 Visits)	**Drug A**	**Drug B**	**p-Value**	**Odds Ratio (OR)**
ESA Rescue				
Total Amount	1	87	0.0005215*	0.07696385
% of Subjects	10%	87.5%		
ESA Rescue with Drug A				
Total Amount	1	60	0.008653*	0.1115777
% of Subjects	10%	87.5%		
Blood Transfusions				
Total Amount	4	4	0.01617	6.579715
% of Subjects	10%	50%		
Iron Supplementations				
Total Amount	24	49	0.0003313*	3.24999
% of Subjects	80%	100%		

*Fisher's Exact Test showed a significant difference between Drug A and B after test for independence and likelihood. An OR > 1 shows that the likelihood of an event is more likely to occur in Drug A than Drug B.

Adverse events (AE) for this study were an important secondary endpoint to determine safety. When comparing AE and SAE occurrence over the 52 weeks, there was not a significant difference between Drug A (ESA) and Drug B (HIF-PH inhibitor). Due to the lack of statistical significance and a small sample size, the conclusion of which drug is safer for the treatment of CKD cannot be inferred.

Drug A (ESA) had 222 AEs and 11 (4.95%) SAEs. Drug B (HIF-PH inhibitor) had 171 AEs and 12 (7.01%) SAEs. The type of SAEs that occurred for Drug A (ESA) were Hypervolemia (Fluid Overload) (18.2%), Hyperkalemia (18.2%), Ischemic Colitis (9.1%), Acute Traumatic Subdural Hematoma (9.1%), Cellulitis (9.1%), Metabolic Derangement (9.1%), Fall (9.1%), and Spinal Fracture (9.1%). The type of SAEs that occurred for Drug B (HIF-PH inhibitor) were Hypervolemia (Fluid Overload) (8.3%), Worsening of Gastroparesis (33.3%), Acute Gastroenteritis (8.3%), Acute Pancreatitis (8.3%), Deep Vein Thrombosis (8.3%), Hospital Acquired Pneumonia (8.3%), and Diverticulitis with Abscess (8.3%). The indication of SAE and the relation to either drug was determined by the PI. Table 11 summarizes this information.

Table 11: Drug A (ESA) and Drug B (HIF-PH Inhibitor) Adverse Events

Wk 52 (17 Visits)	**Drug A**	**Drug B**	**p-Value**
**Total AEs*	222	171	0.5178
Total SAEs	11 (4.95%)	12 (7.01%)	
Subcategories	*Percentage of SAEs were determined out of the number of total AEs		
Hypervolemia (Fluid Overload)	2 (18.2%)*	1 (8.3%)*	
Hyperkalemia	2 (18.2%)	-	
Ischemic Colitis	1 (9.1%)	-	
Worsening of Gastroparesis	-	4 (33.3%)	
Acute Gastroenteritis	-	1 (8.3%)	
Acute Pancreatitis	-	1 (8.3%)	
Deep Vein Thrombosis	-	1 (8.3%)	
Hospital Acquired Pneumonia	-	1 (8.3%)	
Acute Traumatic Subdural Hematoma	1 (9.1%)	-	
Diverticulitis with Abscess	-	1 (8.3%)	
Cellulitis	1 (9.1%)	-	
Metabolic Derangement	1 (9.1%)	-	
Fall	1 (9.1%)	-	
Extremity Syncope	-	1 (8.3%)	
Spinal Fracture	1 (9.1%)*	-	
Toe Infection	-	1 (8.3%)	
Peritoneal Dialysis Tube Malfunction	1 (9.1%)	-	

*SAEs indicated with a star were deemed to not be related to Drug A or Drug B. They were a further complication of the worsening condition of subjects with CKD and their comorbid conditions.

One of the main secondary endpoints of the study was the occurrence of cardiovascular AEs. When comparing the cardiovascular AEs between Drug A (ESA) and B, there was no statistical significance. Drug A (ESA) had more events (19) than Drug B (HIF-PH inhibitor) (7) which has been seen in previous studies. The types of events that occurred with Drug A (ESA) were Worsening of Hypertension (31.5%), Worsening of Arrythmia (5.3%), Worsening of Congestive Heart Failure (5.3%), Worsening of Hypotension (42.0%), Tachycardia (5.3%), Cardiac Murmur (5.3%), and Atherosclerosis (5.3%). The events that occurred with Drug B (HIF-PH inhibitor) were Worsening of Hypertension (28.6%), Worsening of Arrythmia (14.3%), Bradycardia (42.8%), and Atrial Fistulation (14.3%). Drug A (ESA) did have a greater incidence of worsening of hypertension than Drug B (HIF-PH inhibitor), which was expected given the side effects of the medication. Since there was no significant difference between the 2 drugs, it cannot be determined, from this data, whether one drug caused more cardiovascular events than the other, and whether the events reported are clinically significant to the trial as a whole. Table 12 outlines these events.

Table 12: Drug A (ESA) and Drug B (HIF-PH Inhibitor) Cardiovascular Adverse Events

Wk 52 (17 Visits)	**Drug A**	**Drug B**	**p-Value**
Total Cardiovascular AEs	19 (8.56%)	7 (4.09%)	0.1009
Subcategories			
Worsening of Hypertension	6 (31.5%)	2 (28.6%)	
Worsening of Arrythmia	1 (5.3%)	1 (14.3%)	
Worsening of Congestive Heart Failure	1 (5.3%)	-	
Worsening of Hypotension	8 (42.0%)	-	
Tachycardia	1 (5.3%)	-	
Bradycardia	-	3 (42.8%)	
Cardiac Murmur	1 (5.3%)	-	
Atherosclerosis	1 (5.3%)	-	
Atrial Fistulation	-	1 (14.3%)	

Discussion

The successful management of CKD has been a difficult issue to deal with. With the advent of ESAs, a couple of decades ago, there appeared to have been a brighter outcome for this multifaceted disease. As more research was done on these treatments, however, it was discovered that they may cause more harm than good. With ESAs causing an increase in cardiovascular incidences and death, as well as possibly exacerbating the main problem that occurs with CKD, anemia, it became apparent that a new method of treatment was needed. Although this new method has only been researched over the last few years, the data presented here gives some insight into how this drug may ultimately perform in the end.

Despite the small sample size and short timeline, a few key results highlighted the significance of this study. In regard to Hb levels throughout the 52-week period, there were effective or acclimated periods of time in which Hb levels were maintained. In both Drug A (ESA) and Drug B (HIF-PH inhibitor), Hb could be seen to be higher and within range during the efficacy periods with a significant increase during Efficacy Period 1 for Drug B (HIF-PH inhibitor). This outcome could be the effect of the dose and pharmacokinetic properties of each drug during this time, but those factors would have to be explored outside of this report. From Baseline to the End of Treatment there was a significant difference in the Hb levels for both drugs, suggesting that Drug A (ESA) and Drug B (HIF-PH inhibitor) are effective at increasing Hb levels within range with Drug A (ESA) being more likely to do so. The distribution of Hb levels between subjects may also vary between the 2 drugs based on a variety of factors. In respect to the dosing of Drugs A and B, there was a significant difference between interrupted doses of Drug A (ESA) versus Drug B (HIF-PH inhibitor) with Drug B (HIF-PH inhibitor) having more interruptions due to those subject's increased need for supplementation which was

also significantly different. There was not a significant difference in any of the AEs that occurred with the 2 drugs, indicating that the side effects encountered with the administration of these 2 drugs are similar.

Drug B (HIF-PH inhibitor) has both benefits and downfalls, but it is apparent that the benefits carry more weight. It has been shown, through this small section of data, to be effective in increasing Hb values from Baseline (primary endpoint), and therefore managing the anemia, with fewer dosing changes when compared to Drug A (ESA). These fewer dosing changes allow for patients to take the drug in a manner that would require fewer doctor visits and dosing stabilization to reach a degree of Hb homeostasis. Drug B (HIF-PH inhibitor) also had fewer AEs and cardiovascular AEs and more supplementation requirements than Drug A (ESA) (secondary endpoints), but the determination of the cause of the increased supplementation need and clinical significance cannot be determined based on this small sample size. In terms of efficacy, Drug B (HIF-PH inhibitor) can be effective at reaching target Hb levels, but maintenance of the anemia over long periods of time may be an issue due to the fluctuations that occurs with this drug. In relation to safety, Drug B (HIF-PH inhibitor) caused less overall AEs, especially cardiovascular AEs, showing that this drug may be safer than the current standard of care. Overall, Drug B (HIF-PH inhibitor) has the ability to become the new standard of care, but a larger sample size needs to be investigated to definitively prove its success.

CHAPTER VI

SUMMARY AND CONCLUSION

Limitations

For this particular research study, there were quite a few limitations that were encountered. The main limitations were the small sample size for the study and the study time frame in which retrospective data was available to compare all subjects involved in the study. At this site, the total enrollment was 26 subjects with 18 reaching the necessary time point of 52-weeks for this analysis. Subjects also had to be within the 8.0 g/dL to 11.0 g/dL Hb range to qualify for the study which made establishing overall baseline difficult. Since this was a randomized study, unequal data sets occurred between the 2 drugs which made data comparison a challenge. The total duration of enrollment for the study was four years long, so not all subjects were on the same study week. While analyzing the completed data, 52 weeks or the one-year mark appeared to be a time point where most study subjects had successfully completed the study end points with sufficient data to analyze. This stopping point was also deemed as the end of treatment period 2.

Another limitation of this study was that the records were paper based and were later transferred to an online system. If any data points were missing or illegible, it could cause errors in data analysis. Since this data was in a transition period, some information was accessed

through the paper source and some through the online source. This initially caused problems in finding and determining the accuracy of information.

Obtaining data from patients and accurate transcription and documentation of that information by study staff is a major limitation for most clinical trials. For example, a subject could report a particular AE, but study staff could fail to correctly record that information or mark its severity or relation to study drug. This limitation could make it difficult to assess efficacy and safety of the drugs being studied.

In relation to the safety and efficacy evaluations of this trial, a major limitation is the overall initial health of the subject's involved. Due to the severely vulnerable and volatile nature of these subjects' health, AEs, hospitalization, and death causes breaks in treatment and effects the flow of the study. With a break in study, the drugs are interrupted, and overall efficacy cannot be truly evaluated because the continuation of the drug is not possible in these situations. Also, these subjects are in a declining state of health, making judgement of safety complicated.

The final limitation of this study was the fact that this data is just a small portion of the overall data being collected in this worldwide, multicenter clinical trial. With that information, this data cannot be considered as an overall determination of these drugs and their impact on the indicated condition. It cannot be said for sure what the outcome of this new drug is, until all data from all subjects enrolled has been sufficiently analyzed.

Future Directions

For this particular set of data, uploading paper source to online source is still in progress. This shift in source will allow for better and more accurate data collection and have it easier to find and access important trial information of subjects.

Although the collection of data for this part of the study has been concluded, the clinical trial is still on-going and in the observational period. Subjects are still coming in for visits and the same procedures are being followed. At the end of the study, all the data from the site will be sent, collected, and analyzed by the sponsor's data management team and the final outcome of the trial released to the public. If the data is sufficient in proving that Drug B (HIF-PH inhibitor) is safe and effective in maintaining Hb levels and decreasing AEs, especially cardiovascular AEs, then another phase III trial may begin under other primary endpoints, or phase IV initiation may begin.

Conclusion

Overall, CKD is a serious and debilitating disease especially when anemia develops. The standard of care and the new novel treatment both have their pros and cons when it comes to managing the Hb fluctuations that occur during the course of this disease. With this particular research, it cannot be definitively said whether or not the entire primary and secondary endpoints have been met or hypothesis proven for Drug B (HIF-PH inhibitor) since it is just a small sample of the complete trial, but the endpoints have been observed enough to reach the possible conclusions outlined above. Although for this section of research, it can be said that Drug B (HIF-PH inhibitor) worked better in some endpoints than Drug A (ESA) for this particular cohort of subjects, but further evaluation is necessary.

CHAPTER VII

INTERNSHIP EXPERIENCE

My internship took place at Sunbeam Clinical Research at their Heartbeat Clinic site in McKinney, Texas as well as their Texas Renal Care site in Greenville, Texas. Dr. Sami Alam acted as my mentor and Dr. Adeel Ijaz as the Primary Investigator. I performed this research under the tutelage of Omar Siddiq, Kiran Asma, and Kamran Quddusi as clinical research coordinators. I had the privilege of participating in various clinical trials during the course of my internship including:

I. RESTORE trial: A clinical study of patients with symptomatic neuRogenic orthostatic hypotEnsion to assess Sustained effecTs Of dRoxidopa thErapy (Phase IV)
II. FSGS Trial: Randomized, Multicenter, Double-Blind, Parallel, Active-Control Study of the Effects of Sparsentan, a Duel Endothelin Receptor and Angiotensin Receptor Blocker, on Renal Outcomes in Patients with Primary Focal Segmental Glomerulosclerosis (Phase III)
III. CR845 Trial: A Study to Evaluate the Safety and Effectiveness of CR845 in Hemodialysis Patients with Moderate-to-Severe Pruritus (Phase III)

In addition to the running of clinical trial experience I acquired during this internship, I also participated in site qualification visits (SQV), site initiation visits (SIV), and pre-site selection visits (PSV).

Throughout this internship, I performed the following duties:

1. Participating in other studies listed above:
    a. Subject recruitment, enrollment, and screening
    b. Trial study visits and documentation
    c. IP Accountability
    d. Data organization and reporting
    e. eSource and paper source organization
    f. Maintenance of eRegulatory information
    g. Monitoring visits
    h. IRB reporting
2. Attending Meetings/Lunches
    a. Weekly PI Meetings
    b. Monthly Employee Meetings/Lunch
    c. Monthly CRC Meetings
    d. Monthly Staff Training
3. New trial submissions and questionnaires

Journal Summary

On my first day of my internship, I sat in a SIV for the RESTORE trial and within the first few weeks was actively participating in the enrollment and recruitment for this trial. As having never participated in any kind of clinical research, the entire process of recruiting, enrolling, and screening patients was a learning curve that I soon took a hold of. I implemented a checklist and flowchart of how the screening procedures should go and eventually transitioned those methods to other study visits. As I became more comfortable at this trial, I was asked to

attend other SIV, SQV, and PSV. While the internship progressed, and my thesis topic was solidified, I spent an equal amount of time between McKinney assisting in the RESTORE trial and Greenville collecting data and understanding that trial. Throughout this internship experience, a typical week consisted of subject recruitment and enrollment, screening and study visits, eSource documentation, chart reviews, data entry, interaction with staff and study monitors, subject phone calls, and site overview.

APPENDIX A

DAILY INTERNSHIP JOURNAL

Week 1: May 6 – May 10, 2019

Tuesday 5/7/19

- SIV visit with the CRA for Lundbeck RESTORE Study: Met with CRA and Sunbeam Research Staff to discuss the clinical trial, trained on Amendment 5 of the protocol, and was introduced to the various interfaces required for successful completion of the trial.
- Received and signed the Delegation and Training logs at the site.
- Received SC duties and responsibilities while on the trial.
- Received a tour of both the McKinney and Dallas Heartbeat Clinic offices.
- Discussed with Dr. Alam about internship and thesis expectations as well as began the brainstorming process.

Wednesday 5/8/19

- Started training on Real-Time CTMS and became acquainted with the interface and various tabs.

Thursday 5/9/19

- Signed confidentiality agreement.
- Finished training on Real-Time CTMS.
- Setup Firecrest account and completed Firecrest ICH GCP (R2) Training.
- Setup Medidata account and began Medidata training.
- Trained on Microsoft Teams and setup company email and laptop.

Friday 5/10/19

- Completed Medidata Rave EDC Essentials for CRC training.
- Completed Introduction to Medidata training.
- Setup ALMAC account for Droxidopa Clinical Trial.
- Emailed and setup meeting for Research Proposal review.
- Worked on thesis research topics and began literature review.

Week 2: May 13 – May 17, 2019

Monday 5/13/19

- Initialed and signed The Heartbeat Clinic HIPPA policies—HIPPA Training Handbook for the Nursing/Clinical Staff.
- Became acquainted with lab kits and protocol for Visit 1.
- Reviewed and edited informed consent form.
- Reviewed and edited potential subject list for recruitment and enrollment.
- Entered patients into Real-Time CTMS for recruitment and enrollment.
- Sat with Dr. Alam as he explained the trial to interested patients and entered those patients in Real-Time CTMS.
- Added patient appointments to the calendar on Real-Time CTMS.
- Added IRB approval letter, approved ICFs and participant materials to eDOCs in Real-Time CTMS.
- Learned how to navigate patient searches in eClinicalWorks.

Tuesday 5/14/19

- Watched Dr. Alam give informed consent and the consenting signing and copying process.

- Made copies of informed consent for subjects.
- Made screening packets for incoming subjects—patient demographics and MH, informed consent, physical exam form, questionnaires.
- Watched the lead CRC do lab draws and lab processing.
- Did lab processing for subject screening visits and packaged the kits to send to ICON laboratory.
- Scanned in subject documents for online eSource—patient demographics and MH, informed consent, physical exam form, questionnaires.
- Watched the lead CRC input subject data into EDC and Real-Time CTMS.
- Printed out screening packets for subject screening and enrollment for Thursday.

Wednesday 5/15/19

- CRM Internship Orientation.
- Met with Dr. Alam to finalize the 3 thesis topics for the Research Proposal meeting next week.
- Developed the layout and started writing the paper for the Research Proposal—objectives, hypothesis, and background.

Thursday 5/16/19

- Created and organized patient binder.
- Made subject enrollment/screening packets—ICF, questionnaires, medical release forms, W9 forms, physical exam.
- Entered in subject medical history and concomitant medications into eSource in Real-Time CTMS.
- Made ICF copies for subjects and labeled lab kits and requisitions.
- Processed labs for screening visits and packaged for delivery to ICON laboratory.

Friday 5/17/19

- Worked on Research Proposal topics.
- Finished Research Proposal writeup and PowerPoint.

Week 3: May 20 – May 24, 2019

Monday 5/20/19

- Scanned in subject documents—MH, ICF, questionnaires, physical exam, EKG
- Entered subject medical history and concomitant medications
- Started entering subject surgical/procedural history

Tuesday 5/21/19

- Entered lab requisitions and lab reports into subject eSource in Real-TimeCTMS
- Finalized Research Proposal Topics with Dr. Alam
- Entered subject vital signs into eSource in Real-Time CTMS
- Scheduled new subjects for screening

Wednesday 5/22/19

- Answered lab queries
- Entered in subject eSource data in Real-Time CTMS and in Rave EDC for sponsor
- Uploaded subject visit 1 documents to subject documents in Real-Time CTMS
- Made subject enrollment/screening packets—ICF, questionnaires, medical release forms, W9 forms, physical exam

- Added subject appointments to Real-Time calendar

Thursday 5/23/19

- Had Research Proposal Topic Meeting @ Fort Worth UNTHSC
- Assisted with subject screening and enrollment
- Obtained and confirmed subject medical history and concomitant medications
- Entered in subject data to eSource
- Moved subjects from "scheduled for screen" to "enrolled"
- Processed subject labs and packaged for shipping to ICON

Friday 5/24/19

- Answered lab queries
- Worked on new thesis proposal topic

Week 4: May 27 – May 31, 2019 (Vacation)

Week 5: June 3 – June 7, 2019

Monday 6/3/19

- Scanned in subject documents—MH, ICF, questionnaires, physical exam, EKG
- Uploaded subject documents into Real-Time and updated eSource to reflect the updated documents
- Entered subject medical history and concomitant medications into Real-Time and transferred into EDC
- Entered visit 1 and visit 2A data into EDC
- Worked on research proposal first draft
- Acknowledged receipt of IP in Almac portal

Tuesday 6/4/19

- Prepared a list of potential subjects based on inclusion criteria
- Called subjects to update medical history and concomitant medications
- Updated subject eSource and EDC forms
- Finalized Research Proposal First Draft Outline

Wednesday 6/5/19

- Collected data for Research Proposal
- Organized data for Research Proposal
- Updated subject information in eSource
- Worked on Research Proposal First Draft

Thursday 6/6/19

- Conducted subject visit 2b
- Conducted subject visit 2a
- Updated subject eSource documents to reflect current visits
- Updated subject EDC
- Collected and counted IP and re-dispensed as appropriate
- Scheduled subjects for visit 2a

Friday 6/7/19

- Completed Research Proposal First Draft
- Called subjects to schedule visit 2a

- Continued transferring subject information from eSource into EDC

Week 6: June 10 – June 14, 2019

Monday 6/10/19
- Answered outstanding queries in EDC
- Updated subject notebook and made note of missing information that needs to be updated by the subject
- Updated Real-Time CTMS with subject information
- Made appointment reminder phone calls to subjects
- Updated subject visit information for stipend payment
- Called subjects to schedule visit 2a
- Looked at subject qualification documents and uploaded appropriate forms to Real-Time CTMS

Tuesday 6/11/19
- Conducted Visit 2a Titrations
- Conducted Visit 2c Titration
- Went over subject medical history and concomitant medications
- Dispensed and accounted for IMP
- Counted IMP and re-dispensed as appropriate
- Performed and recorded BP measurements
- Updated eSource and EDC as appropriate

Wednesday 6/12/19
- Recruited subjects from subject referral list
- Contacted enrolled subjects to schedule next visits
- Updated eSource and uploaded supporting documents
- Answered queries in EDC
- Updated potential contact list

Thursday 6/13/19
- Continued to update subject eSource and EDC
- Met with potential subjects and scheduled screening visits
- Created visit forms for source documentation
- Met with PI to discuss study progression

Friday 6/14/19
- Called subjects that had visit 2 this week
- Updated subject eSource and EDC
- Requested signatures in Real-Time
- Contacted subjects for screening and 2a visits

Week 7: June 17 – June 21, 2019

Monday 6/17/19
- Organized subject binder
- Created visit packets for the week
- Scheduled screening and 2a visits

- Called subjects for study visit reminders for the week
- Updated Real-Time and EDC
- Answered queries in EDC

Tuesday 6/18/19

- Met with subjects for visit 2 appointment
- Advised subjects on new dosing regime and titrated IP up to the next dosage
- Performed IP accountability, administered study medication, and took vitals
- Updated subject medical history and concomitant medications as necessary
- Updated subject visit information in Real-Time eSource
- Transferred subject eSource to EDC
- Scheduled subjects for next study visit
- Scheduled potential subjects for screening
- Answered queries in EDC
- Met with PI to discuss study progress

Wednesday 6/19/19

- Met with subject in the Dallas office
- Performed visit 2b appointment
- Advised subject on new dosing regime and titrated IP up to the next dosage
- Performed IP accountability, administered study medication, and took vitals
- Updated subject medical history and concomitant medications as necessary
- Updated subject visit information in Real-Time eSource
- Transferred subject eSource into EDC
- Scheduled subject for next study visit
- Made study visit reminder calls
- Rescheduled subjects for next week or the first week in July
- Answered queries in EDC

Thursday 6/20/19

- Answered queries in EDC
- Made copies of paper eSource and organized eSource binder
- Filed subject notes and organized subject binder
- Created visit forms for remote appointments on Friday
- Had employee training at Sunbeam main office in Prosper

Friday 6/21/19

- Performed remote study visits
- Had subjects take their vitals
- Went over IP accountability and new dosing regimen before subject took IP
- Reviewed medical history and concomitant medications and updated as necessary
- Scheduled subjects for next study visit
- Updated subjects eSource information
- Entered eSource for each study visit and transferred into EDC
- Answered queries in EDC

Week 8: June 24 – June 28, 2019

Monday 6/24/19

- Performed remote study visits
- Had subjects take their vitals
- Went over IP accountability and new dosing regimen before subject took IP
- Reviewed medical history and concomitant medications and updated as necessary
- Performed screening visit with subject
- Administered informed consent, questionnaires, took vitals, took medical history and concomitant medications, went over inclusion/exclusion criteria, answered subject questions about the study, and processed labs
- Scheduled subjects for next study visit
- Updated subjects eSource information
- Entered eSource for each study visit and transferred into EDC
- Answered queries in EDC

Tuesday 6/25/19

- Met with subjects for visit 2 appointment
- Advised subjects on new dosing regime and titrated IP up to the next dosage
- Performed IP accountability, administered study medication, and took vitals
- Updated subject medical history and concomitant medications as necessary
- Updated subject visit information in Real-Time eSource
- Transferred subject eSource to EDC
- Scheduled subjects for next study visit
- Reached out to enrolled patients to see if they were still interested in the study
- Answered queries in EDC

Wednesday 6/26/19

- Met with subject in the Dallas office
- Performed visit 2c appointment
- Advised subject on new dosing regime and titrated IP up to the next dosage
- Performed IP accountability, administered study medication, and took vitals
- Updated subject medical history and concomitant medications as necessary
- Updated subject visit information in Real-Time eSource
- Transferred subject eSource into EDC
- Scheduled subject for next study visit
- Answered queries in EDC

Thursday 6/27/19

- Met with subjects in McKinney office
- Performed visit 2 remote study visits and in clinic study visits
- Performed unscheduled visit and processed unscheduled lab kit
- Processed labs and sent off to central laboratory for processing
- Had subjects take their seated vitals and count IP for remote visit and performed in clinic procedures—vitals, IP accountability, IP administration
- Discussed any adverse events and any changes to their medical history or concomitant medications

- Advised subjects on new dosing regime and titrated IP up to next dose
- Updated subject study visit information into eSource
- Transferred subject eSource into EDC
- Scheduled subjects for next study visit
- Answered queries in EDC
- Took Dangerous Goods Training through The Mayo Clinic - Uploaded CV and certifications to eDocs in Real-Time
- Met with the PI to discuss subjects in the trial and to get document signatures

Friday 6/28/19

- Met with subjects remotely
- Had subjects take their vitals and perform IP accountability
- Discussed any adverse events and changes to medical history and concomitant medications
- Advised subjects on new dosing regime and administered IP
- Updated subject study visit information into eSource
- Transferred subject eSource into EDC
- Called subjects for appointment reminders and to see how they were handling
- their new doses
- Spoke with Dr. Alam about the trial and how things were progressing
- Met with the lead CRC in Greenville site to discuss documents necessary for research proposal approval
- Updated research proposal with new information from lead CRC about trial

Week 9: July 1 – July 5, 2019

Monday 7/1/19

- Made and copied visit 3 checklist
- Performed remote visit 2 procedures per protocol
- Had subjects take their vitals and preform IP accountability
- Discussed any adverse event and changes to medical history of concomitant medications and updated as necessary
- Advised subjects on next dosing regime and administered IP over the phone
- Scheduled subjects for next visit
- Called subjects for appointment reminders
- Spoke with sponsor monitor to confirm protocol for visits 3 and 4 and how to request another shipment of IP for the site
- Performed in clinic visit 3 procedures per protocol
- Took subject vitals, administered questionnaires and assessments, reviewed inclusion/exclusion criteria, discussed any adverse events or changes to medical history or concomitant medications, and dispensed and administered IP
- Advised subject on new dosing regime and scheduled next visit
- Entered subject information into eSource and transferred into EDC
- Organized data for thesis
- Scheduled subjects for appointments and called subjects for interest inquiries

- Prepared visit forms for the next day
- Uploaded Temperature Logs for analysis

Tuesday 7/2/19

- Performed remote visit 2 procedures per protocol
- Had subjects take their vitals and preform IP accountability
- Discussed any adverse event and changes to medical history of concomitant medications and updated as necessary
- Advised subjects on next dosing regime and administered IP over the phone
- Scheduled subjects for next visit
- Spoke with monitor and medical monitor about protocol and subject queries
- Performed in clinic visit 3 procedures per protocol
- Took subject vitals, administered questionnaires and assessments, reviewed inclusion/exclusion criteria, discussed any adverse events or changes to medical history or concomitant medications, and dispensed and administered IP
- Advised subject on new dosing regime and scheduled next visit
- Entered subject information into eSource and transferred into EDC
- Prepared visit forms for the next day
- Scanned and uploaded completed and signed questionnaires into subject eSource

Wednesday 7/3/19

- Called subjects to schedule appointments
- Emailed Medical Monitor in regard to subjects in question from the sponsor
- Went through "Not Contacted" subjects in Real-Time and either contacted them to gauge interest in study to schedule for screening or updated the contact attempts from the form in Teams as necessary
- Updated potential subject list
- Performed remote visit 2 procedures per protocol
- Had subjects take their vitals and preform IP accountability
- Discussed any adverse event and changes to medical history of concomitant medications and updated as necessary
- Advised subjects on next dosing regime and administered IP over the phone
- Scheduled subjects for next visit
- Entered subject information into eSource and transferred into EDC

Thursday 7/4/19

- Worked on queries in EDC

Friday 7/5/19

- Performed remote visit 2 procedures per protocol
- Had subjects take their vitals and preform IP accountability
- Discussed any adverse event and changes to medical history of concomitant medications and updated as necessary
- Advised subjects on next dosing regime and administered IP over the phone
- Scheduled subjects for next visit
- Entered subject information into eSource and transferred into EDC
- Answered open queries in EDC

Week 10: July 8 – July 12, 2019

Monday 7/8/19

- Performed remote visit 2 procedures per protocol
- Had subjects take their vitals and preform IP accountability
- Discussed any adverse event and changes to medical history of concomitant medications and updated as necessary
- Advised subjects on next dosing regime and administered IP over the phone
- Scheduled subjects for next visit
- Called subjects for appointment reminders
- Spoke with monitor to monitoring visit for Tuesday
- Entered subject information into eSource and transferred into EDC
- Answered open queries in
- Prepared visit forms for the next day
- Had a meeting with PI in regard to the monitoring visit and open queries in EDC
- Uploaded Temperature Logs for analysis

Tuesday 7/9/19

- Had sponsor monitoring visit
- Answered any outstanding questions from the monitor and corrected items in eSource and EDC
- Performed in clinic visit 3 procedures per protocol
- Took subject vitals, administered questionnaires and assessments, reviewed inclusion/exclusion criteria, discussed any adverse events or changes to medical history or concomitant medications, and dispensed and administered IP
- Advised subject on new dosing regime and scheduled next visit
- Entered subject information into eSource and transferred into EDC
- Prepared visit forms for the next day
- Scanned and uploaded completed and signed questionnaires into subject eSource
- Met with PI and sponsor to discuss visit and clarify any unanswered questions as well as confirm answered queries
- Had inclusion/exclusion criteria training and review of stopping criteria with monitor
- Uploaded monitoring visit forms into eSource

Wednesday 7/10/19

- Called subjects to schedule appointments
- Updated potential subject list
- Performed remote visit 2 procedures per protocol
- Had subjects take their vitals and preform IP accountability
- Discussed any adverse event and changes to medical history of concomitant medications and updated as necessary
- Advised subjects on next dosing regime and administered IP over the phone
- Scheduled subjects for next visit
- Entered subject information into eSource and transferred into EDC
- Answered follow-up questions from monitor
- Answered open queries in EDC

Thursday 7/11/19

- Worked on uploading medical histories to eSource
- Answered open queries in EDC
- Performed screening visit 1 per protocol
- Conducted informed consent process, gave and explained questionnaires, took vitals (BP, HR, Rr, Temp, Weight), obtained medical release form, and gathered medical history and concomitant medication information
- Added all new enrolled subject information into eSource
- Uploaded screening documents to eSource

Friday 7/12/19

- Performed remote unscheduled visit 2 procedures per protocol
- Had subjects take their vitals and preform IP accountability
- Discussed any adverse event and changes to medical history of concomitant medications and updated as necessary
- Advised subjects on next dosing regime and administered IP over the phone
- Scheduled subjects for next visit
- Entered subject information into eSource and transferred into EDC
- Performed adverse event procedure per protocol
- Requested signatures in eSource
- Answered open queries in EDC
- Transferred information from eSource into EDC from screening visit
- Conducted follow-up phone calls with patients on Visit 3

Week 11: July 15 – July 19, 2019

Monday 7/15/19

- Received and confirmed IP shipment
- Put away IP in designated area and checked temperature transport log for any alarms
- Uploaded temperature transport log into eSource and updated sponsor site for receipt of shipment
- Called subjects to check on how they were doing during open label
- Called subjects for appointment reminders
- Performed visit 3 procedures per protocol
- Took subject vitals, administered questionnaires and assessments, reviewed inclusion/exclusion criteria, discussed any adverse events or changes to medical history or concomitant medications, and dispensed and administered IP
- Advised subject on new dosing regime and scheduled next visit
- Entered subject information into eSource and transferred into EDC
- Gathered subject medical history for upload into eSource
- Answered outstanding queries in EDC
- Uploaded Temperature Logs for analysis

Tuesday 7/16/19

- Called subjects to schedule visit 2a
- Pre-screened subjects for study and scheduled those pre-qualified for screening visit 1

- Updated subject eSource
- Answered queries in EDC
- Pulled patient charts for screening visits
- Met with subjects per study doctor's recommendation

Wednesday 7/17/19

- Called subjects to reschedule, schedule, and remind about appointments
- Pulled medical histories for upload into eSource
- Answered emails from study monitors
- Answered queries in EDC
- Updated subject eSource as appropriate
- Prescreened potential subjects from patient database

Thursday 7/18/19

- Answered queries in EDC
- Updated subject eSource as necessary
- Attended monthly company meeting and training
- Met with study doctor to attain signatures and discuss upcoming site qualification visit

Friday 7/19/19

- Made appointment reminder calls
- Called current subjects in treatment period to check on how they are feeling and to assess any adverse events and changes in medical history or concomitant medications
- Answered queries in EDC and updated subject eSource as necessary
- Uploaded signature pages for current subjects

Week 12: July 22 – July 26, 2019

Monday 7/22/19

- Performed screening procedures per protocol
- Administered informed consent, took subject vitals, administered study questionnaires and assessments, reviewed inclusion/exclusion criteria, completed medical history and concomitant medication documentation, overviewed adverse events, processed and mailed out labs, scheduled subject for next visit
- Called subjects for appointment reminders
- Reschedule subjects for appointments as necessary
- Ordered laboratory kits for visit 1 and 6
- Performed visit 2a procedures per protocol
- Took subject vitals, administered questionnaires and assessments, reviewed inclusion/exclusion criteria, discussed any adverse events or changes to medical history or concomitant medications, and dispensed and administered IP
- Advised subject on new dosing regime and scheduled next visit
- Entered subject information into eSource and transferred into EDC
- Uploaded Temperature Logs for analysis
- Uploaded updated study forms and documents from sponsor portal into study eDocs
- Emailed in-house monitor about study visit 4 questions

Tuesday 7/23/19

- Performed visit 4 procedures per protocol
- Took subject vitals, administered questionnaires and assessments, discussed any adverse events or changes to medical history or concomitant medications, dispensed and administered IP
- Advised subject on new dosing regime and scheduled next visit
- Entered subject information into eSource and transferred into EDC
- Answered queries in EDC

Wednesday 7/24/19

- Performed visit 2 procedures per protocol
- Had subject take their vitals, count their pills, also discussed any adverse events or changes to medical history or concomitant medications, and dispensed and administered IP
- Advised on new dosing regimen and scheduled next visit
- Answered queries in EDC
- Updated regulatory binder
- Entered subject information into eSource and transferred unto EDC
- Calculated subject IP compliance score
- Conducted adverse event reporting

Thursday 7/25/19

- Checked on subject that had an AE and scheduled an in-clinic appointment
- Updated eSource and EDC
- Called subjects to check in with their symptoms and to address any concerns
- Conducted adverse event reporting
- Finished calculating subject compliance scores
- Answered queries in EDC
- Met with PI to obtain signatures and to discuss trial updates and progression
- Scheduled site qualification visit for new study at site
- Dispensed new study medication and uploaded documents to eSource
- Registered and put away new study medication per protocol

Friday 7/26/19

- Performed visit 2 procedures per protocol
- Had subject take their vitals, count their pills, also discussed any adverse events or changes to medical history or concomitant medications, and dispensed and administered IP
- Advised on new dosing regimen and scheduled next visit
- Answered queries in EDC
- Uploaded study documents to patient eSource

Week 13: July 29 – August 2, 2019

Monday 7/29/19

- Performed visit 2 procedures per protocol
- Had subject take their vitals, count their pills, also discussed any adverse events or changes to medical history or concomitant medications, and dispensed and administered IP
- Advised on new dosing regimen and scheduled next visit
- Answered queries in EDC
- Entered subject information into eSource and transferred into EDC
- Met with PI to obtain signatures and to discuss trial updates and progression
- Scheduled site qualification visit for new study at site
- Pre-screened potential subjects from database
- Uploaded temperature logs
- Started organizing data for thesis

Tuesday 7/30/19

- Performed visit 2a procedures per protocol
- Took vitals, administered questionnaires and assessments, reviewed inclusion/exclusion criteria as well as medical history and concomitant medications, and dispensed and administered IP
- Advised subject on dosing regimen and scheduled next visit
- Entered subject and visit information into eSource and transferred into EDC
- Uploaded supporting visit documents to eSource
- Called study monitor to answer information about recent emails
- Called study lab to expediate shipping on lab kits
- Scheduled subjects for screening visits
- Met with PI to discuss AE and dosing changes for a particular subject
- Continued organizing data for thesis

Wednesday 7/31/19

- Performed visit 4 procedures per protocol
- Took vitals, administered questionnaires and assessments, reviewed inclusion/exclusion criteria as well as medical history and concomitant medications, reviewed any AEs, and dispensed and administered IP
- Advised subject on dosing regimen and scheduled next visit
- Performed visit 2 procedures per protocol
- Took vitals, counted pills and IP compliance, discussed any adverse events or changes to medical history or concomitant medications, and administered IP
- Advised subject in dosing regimen and scheduled next visit
- Entered subject and visit information into eSource and transferred into EDC
- Uploaded supporting visit documents to eSource
- Prepared for screening visits
- Answered open queries

Thursday 8/1/19

- Performed visit 4 procedures per protocol
- Took vitals, administered questionnaires and assessments, reviewed inclusion/exclusion criteria as well as medical history and concomitant medications, reviewed any AEs, and dispensed and administered IP
- Advised subject on dosing regimen and scheduled next visit
- Performed visit 2 procedures per protocol
- Took vitals, counted pills and IP compliance, discussed any adverse events or changes to medical history or concomitant medications, and administered IP
- Advised subject in dosing regimen and scheduled next visit
- Performed screening visits per protocol
- Administered consent, issued questionnaires, performed standing test, and registered subjects into sponsor portal
- Entered subject and visit information into eSource and transferred into EDC
- Uploaded supporting visit documents to eSource
- Answered open queries
- Worked on thesis

Friday 8/2/19

- Performed remote visit 2 procedures per protocol
- Had subject take their vitals, count their pills, reviewed any adverse events and changes to medical history or concomitant medications, and administered IP
- Advised subject on dosing regimen and scheduled next visit
- Entered subject and visit information into eSource and transferred into EDC
- Answered open queries
- Worked on thesis

Week 14: August 5 – August 9, 2019

Monday 8/5/19

- Talked to scheduling nurse about Monitor Visit and placement for monitor at the site
- Created visit packets for the day
- Performed remote visit 2 procedures per protocol
- Had subjects take their vitals and count their pills
- Went over any adverse events or changes to medical history or concomitant medications
- Performed IP accountability and compliance, advising subjects on new dosing regimen and scheduled next visit
- Entered data into eSource and transferred into EDC
- Answered open queries in EDC
- Spoke with on-site mentor about thesis and data collection
- Updated eSource and patient binder
- Made appointment reminder and follow-up phone calls to subjects
- Uploaded temperature logs for analysis

Tuesday 8/6/19

- Performed screening visit procedures per protocol
- Administered informed consent, took subject vitals, administered study questionnaires and assessments, reviewed inclusion/exclusion criteria, completed medical history and concomitant medication documentation, overviewed adverse events, processed and mailed out labs, scheduled subject for next visit
- Preformed visit 4 procedures per protocol
- Took subject vitals, administered questionnaires and assessments, discussed any adverse events or changes to medical history or concomitant medications, dispensed and administered IP
- Entered information into eSource and transferred into EDC
- Scheduled subjects for next visit
- Uploaded necessary documents to eSource

Wednesday 8/7/19

- Performed remote visit 2 procedures per protocol
- Had subjects take their vitals and count their pills
- Went over any adverse events or changes to medical history or concomitant medications
- Performed IP accountability and compliance, advising subjects on new dosing regimen and scheduled next visit
- Finished uploading documents to eSource
- Had monthly meeting with research director
- Answered queries in EDC
- Made visit reminder calls

Thursday 8/8/19

- Performed screening visit procedures per protocol
- Administered informed consent, took subject vitals, administered study questionnaires and assessments, reviewed inclusion/exclusion criteria, completed medical history and concomitant medication documentation, overviewed adverse events, processed and mailed out labs, scheduled subject for next visit
- Preformed visit 4 procedures per protocol
- Took subject vitals, administered questionnaires and assessments, discussed any adverse events or changes to medical history or concomitant medications, dispensed and administered IP
- Entered information into eSource and transferred into EDC
- Scheduled subjects for next visit
- Uploaded necessary documents to eSource
- Organized binders
- Met with PI to obtain signatures and discuss trial progress
- Answered queries
- Uploaded documents to eReg binder
- Worked on thesis data

Friday 8/9/19

- Performed remote visit 2 procedures per protocol
- Had subjects take their vitals and count their pills
- Went over any adverse events or changes to medical history or concomitant medications

- Performed IP accountability and compliance, advising subjects on new dosing regimen and scheduled next visit
- Entered data into eSource and transferred into EDC
- Answered open queries in EDC
- Scanned and uploaded signed documents to eSource
- Ordered pregnancy tests from sponsor lab portal
- Made appointment reminder calls for subjects that are scheduled for Monday
- Emailed medical monitor for decision on rescreening approval
- Corrected visits in Real-Time and submitted for QC monitoring
- Completed subject IP accountability logs
- Worked on thesis data and introduction

Week 15: August 12 – August 16, 2019

Monday 8/12/19

- Created visit packets for the day
- Performed remote visit 2 procedures per protocol
- Had subjects take their vitals and count their pills
- Went over any adverse events or changes to medical history or concomitant medications
- Performed IP accountability and compliance, advising subjects on new dosing regimen and scheduled next visit
- Performed screening visit procedures per protocol
- Administered informed consent, took subject vitals, administered study questionnaires and assessments, reviewed inclusion/exclusion criteria, completed medical history and concomitant medication documentation, overviewed adverse events, processed and mailed out labs, scheduled subject for next visit
- Preformed visit 4 procedures per protocol
- Took subject vitals, administered questionnaires and assessments, discussed any adverse events or changes to medical history or concomitant medications, dispensed and administered IP
- Entered data into eSource and transferred into EDC
- Uploaded necessary documents into eSource
- Answered open queries in EDC
- Made appointment reminder and follow-up phone calls to subjects
- Uploaded temperature logs for analysis
- Prepared for monitoring visit
- Confirmed IP shipment and entered it into sponsor system

Tuesday 8/13/19

- Had monitor on site
- Updated eSource and EDC
- Answered monitor queries and questions
- Communicated with study team and sponsor about study related issues
- Met with monitor and query to review study progress and get questions resolved

Wednesday 8/14/19

- Had monitor on site
- Updated eSource and EDC
- Answered monitor queries and questions
- Made visit reminder calls
- Met with monitor to close out the visit and discuss tasks until next monitoring visit

Thursday 8/15/19

- Prepared visit packets for the day
- Performed visit 2a procedures per protocol
- Took subject vitals, administered questionnaires and assessments, reviewed inclusion/exclusion criteria, discussed any adverse events or changes to medical history or concomitant medications, and dispensed and administered IP
- Advised subject on new dosing regime and scheduled next visit
- Entered subject information into eSource and transferred into EDC
- Uploaded study documents to eSource
- Made visit reminder calls
- Answered queries in EDC
- Sent out follow up letters to subjects lost to follow up

Friday 8/16/19

- Finished data collection for thesis in Greenville

Week 16: August 19 – August 23, 2019

Monday 8/19/19

- Created visit packets for the day
- Performed remote visit 2 procedures per protocol
- Had subjects take their vitals and count their pills
- Went over any adverse events or changes to medical history or concomitant medications
- Performed IP accountability and compliance, advising subjects on new dosing regimen and scheduled next visit
- Performed visit 3 procedures per protocol
- Took vitals, administered IP, performed IP accountability and compliance, administered questionnaires, and reviewed concomitant medications and medical history
- Advised subjects on new dosing regimen and scheduled next visit
- Entered data into eSource and transferred into EDC
- Uploaded necessary documents into eSource
- Answered open queries in EDC
- Made appointment reminder and follow-up phone calls to subjects
- Uploaded temperature logs for analysis
- Updated regulatory eSource logs as necessary
- Worked on thesis

Tuesday 8/20/19

- Created visit packets for the day
- Preformed visit 5 procedures per protocol
- Took subject vitals, administered questionnaires and assessments, discussed any adverse events or changes to medical history or concomitant medications, dispensed and administered IP
- Entered data into eSource and transferred into EDC
- Uploaded necessary documents into eSource
- Answered open queries in EDC
- Made recruitment calls to potential subjects
- Worked on thesis

Wednesday 8/21/19

- Finished collecting thesis data
- Entered thesis data into spreadsheet and started in statistical analysis
- Answered open queries
- Updated eSource
- Made visit reminder and follow-up calls

Thursday 8/22/19

- Performed visit 2 procedures per protocol
- Took subject vitals, discussed any adverse events or changes to medical history or concomitant medications, performed IP accountability, administered IP, and advised on new dosing schedule
- Entered data into eSource and transferred into EDC
- Attended monthly employee meeting and lunch
- Met with PI to discuss the trial and obtain signatures
- Worked on thesis

Friday 8/23/19

- Scanned and uploaded eSource documents
- Answered open queries
- Entered data into eSource and transferred into EDC
- Made visit reminder calls
- Worked on thesis

Week 17: August 26 – August 30, 2019

Monday 8/26/19

- Performed visit 2 procedures per protocol
- Took subject vitals, discussed any adverse events or changes to medical history or concomitant medications, performed IP accountability, administered IP, and advised on new dosing schedule
- Entered data into eSource and transferred into EDC
- Prepared for site qualification visit
- Performed visit 3 reassessment by administering questionnaires and dispensing IP
- Uploaded temperature logs
- Submitted necessary documentation to the IRB

- Worked on thesis
- Resolved open queries

Tuesday 8/27/19

- Completed screening procedures per protocol
- Attended Site Qualification Visit in Dallas and McKinney

Wednesday 8/28/19

- Performed visit 5 procedures per protocol
- Took subject vitals, administered questionnaires and assessments, discussed any adverse events or changes to medical history or concomitant medications, dispensed and administered IP
- Entered information into eSource and transferred into EDC
- Scheduled subjects for next visit
- Uploaded necessary documents to eSource
- Answered open queries
- Worked on thesis

Thursday 8/29/19

- Performed visit 2 procedures per protocol
- Took subject vitals, discussed any adverse events or changes to medical history or concomitant medications, performed IP accountability, administered IP, and advised on new dosing schedule
- Entered data into eSource and transferred into EDC
- Scheduled next study visit
- Answered open queries
- Worked on SQV forms and documentation
- Submitted necessary documentation to the IRB
- Worked on thesis

Friday 8/30/19

- Made visit reminder calls
- Answered open queries
- Updated eSource and EDC as appropriate
- Worked on thesis

Week 18: September 2 – September 6, 2019

Monday 9/2/19

- Labor Day Holiday

Tuesday 9/3/19

- Performed site IP accountability and inventory
- Performed visit 5 procedures per protocol
- Took subject vitals, administered questionnaires and assessments, discussed any adverse events or changes to medical history or concomitant medications, dispensed and administered IP
- Performed visit 2 procedures per protocol

- Took subject vitals, discussed any adverse events or changes to medical history or concomitant medications, performed IP accountability, administered IP, and advised on new dosing schedule
- Entered information into eSource and transferred into EDC
- Scheduled subjects for next visit
- Uploaded necessary documents to eSource
- Answered open queries
- Uploaded weekly temperature logs
- Worked on thesis background

Wednesday 9/4/19

- Made study recruitment calls
- Scheduled screening visits
- Answered open queries
- Met with Director of Clinical Research for monthly meeting

Thursday 9/5/19

- Performed visit 3 procedures per protocol
- Took subject vitals, administered questionnaires and assessments, reviewed inclusion/exclusion criteria, discussed any adverse events or changes to medical history or concomitant medications, and dispensed and administered IP
- Performed visit 5 procedures per protocol
- Took subject vitals, administered questionnaires and assessments, discussed any adverse events or changes to medical history or concomitant medications, dispensed and administered IP
- Entered information into eSource and transferred into EDC
- Scheduled subjects for next visit
- Uploaded necessary documents to eSource
- Answered open queries
- Worked on thesis

Friday 9/6/19

- Answered open queries
- Updated eSource as necessary
- Made visit reminder calls
- Worked on thesis

Week 19: September 9 – September 13, 2019

Monday 9/9/19

- Prepared visit packets for the day
- Performed screening visit procedures per protocol
- Administered informed consent, took subject vitals, administered study questionnaires and assessments, reviewed inclusion/exclusion criteria, completed medical history and concomitant medication documentation, and overviewed adverse events
- Preformed visit 4 procedures per protocol

- Took subject vitals, administered questionnaires and assessments, discussed any adverse events or changes to medical history or concomitant medications, dispensed and administered IP
- Scheduled subjects for their next visit
- Entered data into eSource and transferred into EDC
- Uploaded necessary documents into eSource
- Answered open queries in EDC
- Met with PI for trial update and signatures
- Worked on thesis

Tuesday 9/10/19

- Made study recruitment calls
- Made follow-up calls
- Uploaded necessary documents to eSource
- Answered open queries
- Worked on thesis

Wednesday 9/11/19

- Worked on information for follow-up from SQV
- Made recruitment calls
- Made follow-up calls
- Made visit reminder calls
- Worked on thesis

Thursday 9/12/19

- Prepared visit packets for the day
- Performed screening visit procedures per protocol
- Administered informed consent, took subject vitals, administered study questionnaires and assessments, reviewed inclusion/exclusion criteria, completed medical history and concomitant medication documentation, overviewed adverse events, processed and mailed out labs, scheduled subject for next visit
- Entered data into eSource and transferred into EDC
- Uploaded necessary documents into eSource
- Worked on thesis

Friday 9/13/19

- Made study recruitment calls
- Made follow-up calls
- Uploaded necessary documents to eSource
- Answered open queries
- Made visit reminder calls
- Worked on thesis

Week 20: September 16 – September 20, 2019

Monday 9/16/19

- Prepared visit packets for the day
- Uploaded temperature logs

- Performed Visit 5 procedures per protocol
- Took subject vitals, administered questionnaires and assessments, discussed any adverse events or changes to medical history or concomitant medications, dispensed and administered IP
- Performed screening visit procedures per protocol
- Administered informed consent, took subject vitals, administered study questionnaires and assessments, reviewed inclusion/exclusion criteria, completed medical history and concomitant medication documentation, overviewed adverse events, processed and mailed out labs
- Scheduled subjects for their next visit
- Entered data into eSource and transferred into EDC
- Uploaded necessary documents into eSource
- Answered open queries in EDC
- Worked on thesis

Tuesday 9/17/19

- Attended Retrophin-Duplex SIV in Sherman, TX

Wednesday 9/18/19

- Made recruitment calls
- Made follow-up calls
- Made visit reminder calls
- Scheduled new study visits
- Worked on thesis

Thursday 9/19/19

- Performed visit 6 procedures per protocol
- Took subject vitals, administered questionnaires and assessments, discussed any adverse events or changes to medical history or concomitant medications, dispensed and administered IP
- Scheduled subjects for their next visit
- Entered data into eSource and transferred into EDC
- Uploaded necessary documents into eSource
- Attended Sunbeam Employee Monthly Meeting

Friday 9/20/19

- Made recruitment calls
- Made follow-up calls
- Made visit reminder calls
- Scheduled new study visits
- Worked on thesis

Week 21: September 23 – September 27, 2019

Monday 9/23/19

- Prepared visit packets for the day
- Uploaded temperature logs
- Performed Visit 2a procedures per protocol

- Took subject vitals, administered questionnaires and assessments, discussed any adverse events or changes to medical history or concomitant medications, dispensed and administered IP
- Scheduled subjects for their next visit
- Entered data into eSource and transferred into EDC
- Uploaded necessary documents into eSource
- Answered open queries in EDC
- Worked on thesis

Tuesday 9/24/19

- Made recruitment calls
- Made follow-up calls
- Made visit reminder calls
- Scheduled new study visits
- Worked on thesis

Wednesday 9/25/19

- Made recruitment calls
- Made follow-up calls
- Made visit reminder calls
- Scheduled new study visits
- Worked on thesis

Thursday 9/26/19

- Made recruitment calls
- Made follow-up calls
- Made visit reminder calls
- Scheduled new study visits
- Worked on thesis

Friday 9/27/19

- Made recruitment calls
- Made follow-up calls
- Made visit reminder calls
- Scheduled new study visits
- Worked on thesis

Week 22: September 30 – October 4, 2019

Monday 9/30/19

- Worked on thesis data
- Edited thesis
- Made appointment reminder calls
- Answered open queries in EDC
- Made visit packets for the week
- Uploaded temperature logs
- Met with PI for trial update and signatures

Tuesday 10/1/19

- Performed randomization visit per protocol
- Sent out lab kits to ICON
- Performed screening visit per protocol
- Uploaded documents to eSource and transferred to EDC
- Scheduled next visit appointments
- Performed IP accountability and dispensation
- Had lunch meeting with PI and Research Director
- Continued to edit and finalize thesis data and information

Wednesday 10/2/19

- Had 1:1 meeting with Research Director
- Mad subject recruitment and follow-up calls
- Made appointment reminder calls
- Answered open queries in EDC
- Continued to edit and finalize thesis data and information
- Submitted first draft of thesis to major professor

Thursday 10/3/19

- Performed visit 7 per protocol
- Uploaded documents to eSource and transferred to EDC
- Scheduled next visit appointments
- Performed IP accountability and dispensation
- Continued to edit and finalize thesis data and information

Friday 10/4/19

- Attended pre-site qualification visit in Ardmore, OK

Week 23: October 7 – October 11, 2019

Monday 10/7/19

- Uploaded Temperature Logs
- Made visit reminder calls
- Performed visit 2b, 2a, 5, and 2e per protocol
- Performed IP accountability and dispensation
- Met with PI to discuss monitoring visit
- Entered data in eSource and transferred to EDC
- Scheduled subjects for next study visit

Tuesday 10/8/19

- Had monthly monitoring visit
- Performed visit 2a and 4 per protocol
- Met with PI to discuss monitoring visit
- Entered data in eSource and transferred to EDC
- Scheduled subjects for next study visit

Wednesday 10/9/19

- Had monthly monitoring visit
- Went over monitor duties and queries

Thursday 10/10/19

- Made recruitment and follow-up calls
- Answered open queries in EDC
- Entered information about SAEs
- Updated eSource and EDC

Friday 10/11/19

- Made recruitment and follow-up calls
- Made visit reminder calls
- Answered open queries in EDC
- Performed Remote Titration Visits
- Entered data in eSource and transferred to EDC
- Scheduled subjects for next study visit
- Started on thesis defense presentation

Week 24: October 14 – October 18, 2019

Monday 10/14/19

- Uploaded Temperature Logs
- Made visit reminder calls
- Performed visit 2e and Visit 3 per protocol
- Performed IP accountability and dispensation
- Entered data in eSource and transferred to EDC
- Finished entering SAE data
- Answered open queries in EDC
- Scheduled subjects for next study visit

Tuesday 10/15/19

- Performed visit 2a and 2e visits per protocol
- Performed visit 7 and 12 per protocol
- Entered data in eSource and transferred to EDC
- Scheduled subjects for next study visit

Wednesday 10/16/19

- Performed visit 6 per protocol
- Entered data in eSource and transferred to EDC
- Answered open queries in EDC
- Worked on thesis edits and defense presentation

Thursday 10/17/19

- CARA Pharmaceuticals SIV in Greenville, TX

Friday 10/18/19

- Was at home sick with strep
- Worked on thesis edits and defense presentation

Week 25: October 21 – October 25, 2019

Monday 10/21/19

- Worked on thesis defense presentation

Tuesday 10/22/19

- Administered updated ICF to current subjects
- Performed visit 2c, 2d, and 2h visits per protocol
- Performed visit 8 and 12 per protocol
- Entered data in eSource and transferred to EDC
- Uploaded necessary documents to eSource
- Scheduled subjects for next study visit
- Met with PI for signatures and study updates

Wednesday 10/23/19

- Answered open queries in EDC
- Updated eSource and EDC as necessary
- Worked thesis defense presentation

Thursday 10/24/19

- Attended monthly Sunbeam employee meeting and lunch

Friday 10/25/19

- Performed visit 2e per protocol
- Worked on thesis edits and defense presentation

Week 26: October 28 – November 1, 2019

Monday 10/28/19

- Answered emails and queries
- Performed Visit 2d per protocol
- Entered data in eSource and transferred to EDC
- Scheduled subjects for next study visit
- Met with PI for study updates
- Worked on thesis defense presentation

Tuesday 10/29/19

- Had first remote monitoring visit
- Administered updated ICF to current subjects
- Performed visits 5 and 8 per protocol
- Entered data in eSource and transferred to EDC
- Uploaded necessary documents to eSource
- Scheduled subjects for next study visit
- Met with PI for signatures and study updates
- Worked on thesis defense presentation

Wednesday 10/30/19

- Had defense presentation practice with Dr. Mathew at UNTHSC

Thursday 10/31/19

- Performed visits 3 and 7 per protocol
- Entered data in eSource and transferred to EDC
- Uploaded necessary documents to eSource
- Scheduled subjects for next study visit

Friday 11/1/19

- Had Thesis Defense at UNTHSC

APPENDIX B

FIGURES AND TABLES

Table 13: Average Hb Pivot Table

Row Labels	Average of Hb baseline (Wk 0)
A	**10.14142012**
0	11.34230769
6.25	11.1
10	10.83333333
12.5	10.4625
15	10.16666667
20	9.879069767
25	10.01818182
30	9.781818182
40	9.843478261
42.5	10.1
50	8.5
60	8.7
80	10.1
100	9.954545455
B	**9.697777778**
0	10.15957447
150	10.325
300	9.153571429
450	9.577777778
600	9.185714286
Grand Total	**9.944407895**

Tables 14-23: 2X2 Tables for Secondary Endpoints

Drug A		**Drug B**	
In-Range Hb Values	Out of Range Hb Values	In-Range Hb Values	Out of Range Hb Values
10 7 4 9 4 11 8 6 6 11 **76**	7 10 13 8 13 6 9 11 11 6 **94**	1 3 10 7 1 4 1 7 **34**	16 14 7 10 15 13 16 10 **101**
Chi-Square Test	*Number of cases in table: 304* *Number of factors: 2* *Test for independence of all factors:* *Chisq = 12.723* *df = 1* *p-value = 0.0003612*		
Fisher's Exact Test for Count Data	*p-value = 0.0004703* *Alternative hypothesis:* *True odds ratio is not equal to 1* *95 percent confidence interval:* *1.444228 4.111440* *Sample estimates:* *Odds Ratio (OR) = 2.420453 > 1*		

Drug A		**Drug B**	
Total AEs	Total SAEs	Total AEs	Total SAEs
222	11	171	12
Chi-Square Test	*Number of cases in table: 416* *Number of factors: 2* *Test for independence of all factors:* *Chisq = 0.6617* *df = 1* *p-value = 0.4159*		
Fisher's Exact Test for Count Data	*p-value = 0.5178* *Alternative hypothesis:* *True odds ratio is not equal to 1* *95 percent confidence interval:* *0.5565473 3.6339919* *Sample estimates:* *Odds Ratio (OR) = 1.41505 > 1*		

Drug A		**Drug B**	
Total Maintenance Dose	Total Dose	Total Maintenance Dose	Total Dose
72	160	50	128
Chi-Square Test	*Number of cases in table: 410* *Number of factors: 2* *Test for independence of all factors:* *Chisq = 0.4178* *df = 1* *p-value = 0.518*		
Fisher's Exact Test for Count Data	*p-value = 0.586* *Alternative hypothesis:* *True odds ratio is not equal to 1* *95 percent confidence interval:* *0.7342447 1.8143759* *Sample estimates:* *Odds Ratio (OR) = 1.151602 > 1*		

Drug A		**Drug B**	
Total Increased Dose	Total Dose	Total Increased Dose	Total Dose
49	160	27	128
Chi-Square Test	*Number of cases in table: 364* *Number of factors: 2* *Test for independence of all factors:* *Chisq = 1.956* *df = 1* *p-value = 0.1619*		
Fisher's Exact Test for Count Data	*p-value = 0.1924* *Alternative hypothesis:* *True odds ratio is not equal to 1* *95 percent confidence interval:* *0.8358094 2.5571741* *Sample estimates:* *Odds Ratio (OR) = 1.450382 > 1*		

Drug A		**Drug B**	
Total Decreased Dose	Total Dose	Total Decreased Dose	Total Dose
12	160	4	128
Chi-Square Test	*Number of cases in table: 304* *Number of factors: 2* *Test for independence of all factors:* *Chisq = 2.3328* *df = 1* *p-value = 0.1267*		
Fisher's Exact Test for Count Data	*p-value = 0.1941* *Alternative hypothesis:* *True odds ratio is not equal to 1* *95 percent confidence interval:* *0.7038185 10.4290324* *Sample estimates:* *Odds Ratio (OR) = 2.393638 > 1*		

Drug A		**Drug B**	
Total Interrupted Dose	Total Dose	Total Interrupted Dose	Total Dose
27	160	47	128
Chi-Square Test	*Number of cases in table: 362* *Number of factors: 2* *Test for independence of all factors:* *Chisq = 8.573* *df = 1* *p-value = 0.003413*		
Fisher's Exact Test for Count Data	*p-value = 0.004029* *Alternative hypothesis:* *True odds ratio is not equal to 1* *95 percent confidence interval:* *0.2602951 0.8020795* *Sample estimates:* *Odds Ratio (OR) = 0.4605648 < 1*		

Drug A		**Drug B**	
Total Interrupted Dose	Total Dose	Total Interrupted Dose	Total Dose
27	160	47	128
Chi-Square Test	*Number of cases in table: 362* *Number of factors: 2* *Test for independence of all factors:* *Chisq = 8.573* *df = 1* *p-value = 0.003413*		
Fisher's Exact Test for Count Data	*p-value = 0.004029* *Alternative hypothesis:* *True odds ratio is not equal to 1* *95 percent confidence interval:* *0.2602951 0.8020795* *Sample estimates:* *Odds Ratio (OR) = 0.4605648 < 1*		

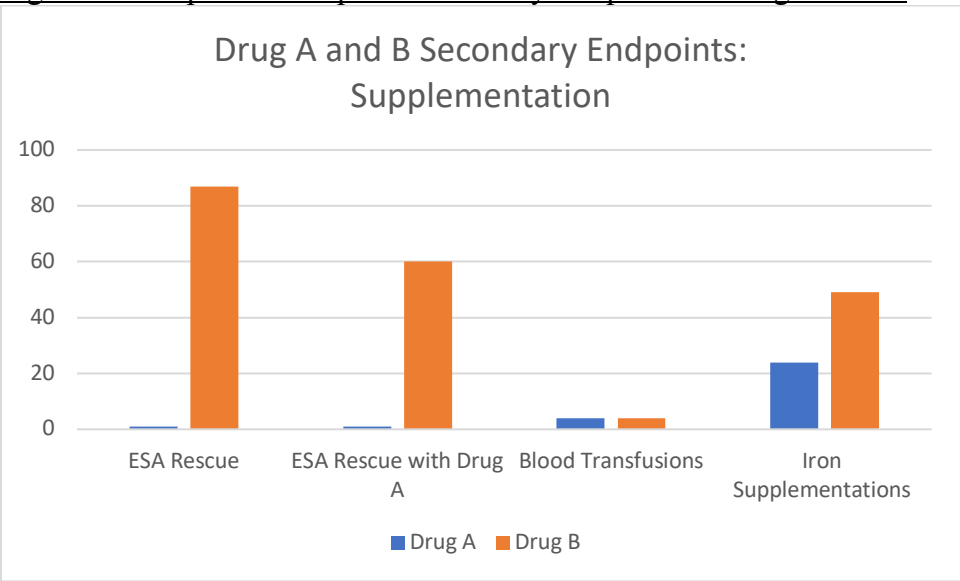
Drug A		**Drug B**	
Total Interrupted Dose	Total Dose	Total Interrupted Dose	Total Dose
27	160	47	128
Chi-Square Test	*Number of cases in table: 362* *Number of factors: 2* *Test for independence of all factors:* *Chisq = 8.573* *df = 1* *p-value = 0.003413*		
Fisher's Exact Test for Count Data	*p-value = 0.004029* *Alternative hypothesis:* *True odds ratio is not equal to 1* *95 percent confidence interval:* *0.2602951 0.8020795* *Sample estimates:* *Odds Ratio (OR) = 0.4605648 < 1*		

Drug A		**Drug B**	
Total Interrupted Dose	Total Dose	Total Interrupted Dose	Total Dose
27	160	47	128
Chi-Square Test	*Number of cases in table: 362* *Number of factors: 2* *Test for independence of all factors:* *Chisq = 8.573* *df = 1* *p-value = 0.003413*		
Fisher's Exact Test for Count Data	*p-value = 0.004029* *Alternative hypothesis:* *True odds ratio is not equal to 1* *95 percent confidence interval:* *0.2602951 0.8020795*		

	Sample estimates: *Odds Ratio (OR) = 0.4605648 < 1*

Drug A		**Drug B**	
Iron Supplementation	Total Supplementation	Iron Supplementation	Total Supplementation
24	30	49	200
Chi-Square Test	*Number of cases in table: 303* *Number of factors: 2* *Test for independence of all factors:* *Chisq = 14.883* *df = 1* *p-value = 0.0001144*		
Fisher's Exact Test for Count Data	*p-value = 0.0003313* *Alternative hypothesis:* *True odds ratio is not equal to 1* *95 percent confidence interval:* *1.661511 6.336343* *Sample estimates:* *Odds Ratio (OR) = 3.24999 > 1*		

Figure 7: Comparison Graph of Secondary Endpoints and Significance



Tables 24 – 29: T-Tests Assuming Unequal Variances

t-Test: Two-Sample Assuming Unequal Variances

	Drug B Hb	*Drug A Hb*
Mean	9.69777778	10.1414201
Variance	1.94424876	1.02339321
Observations	135	169
Hypothesized Mean Difference	0	
df	237	
t Stat	-3.1017552	
P(T<=t) one-tail	0.00107848	
t Critical one-tail	1.65130839	
P(T<=t) two-tail	0.00215696	
t Critical two-tail	1.97002401	

t-Test: Two-Sample Assuming Unequal Variances

	Drug B Baseline to Efficacy 1	*Drug A Baseline to Efficacy 1*
Mean	9.554166667	10.08166667
Variance	2.431471631	1.030336158
Observations	48	60
Hypothesized Mean Difference	0	
df	77	
t Stat	-2.025434428	
P(T<=t) one-tail	0.023144063	
t Critical one-tail	1.664884537	
P(T<=t) two-tail	0.046288126	
t Critical two-tail	1.991254395	

t-Test: Two-Sample Assuming Unequal Variances

	Drug B Efficacy Period 1	*Drug A Efficacy Period 1*
Mean	10.1375	10.21
Variance	1.466793478	0.662310345
Observations	24	30
Hypothesized Mean Difference	0	
df	39	
t Stat	-0.251358487	
P(T<=t) one-tail	0.401428357	
t Critical one-tail	1.684875122	
P(T<=t) two-tail	0.802856714	
t Critical two-tail	2.02269092	

t-Test: Two-Sample Assuming Unequal Variances

	Drug B Efficacy 1 to 2	*Drug A Efficacy 1 to 2*
Mean	9.529166667	9.866666667
Variance	1.325634058	0.929885057
Observations	24	30
Hypothesized Mean Difference	0	
df	45	
t Stat	-1.149323442	
P(T<=t) one-tail	0.128247373	
t Critical one-tail	1.679427393	
P(T<=t) two-tail	0.256494745	
t Critical two-tail	2.014103389	

t-Test: Two-Sample Assuming Unequal Variances

	Drug B Efficacy Period 2	*Drug A Efficacy Period 2*
Mean	10.19166667	10.40666667
Variance	1.279057971	1.394436782
Observations	24	30
Hypothesized Mean Difference	0	
df	50	
t Stat	-0.680654815	
P(T<=t) one-tail	0.249614976	
t Critical one-tail	1.675905025	
P(T<=t) two-tail	0.499229952	
t Critical two-tail	2.008559112	

t-Test: Two-Sample Assuming Unequal Variances

	Drug B Efficacy 2 to Wk 52	*Drug A Efficacy 2 to Wk 52*
Mean	9.486956522	10.25172414
Variance	2.563913043	1.089014778
Observations	23	29
Hypothesized Mean Difference	0	
df	36	
t Stat	-1.981059078	
P(T<=t) one-tail	0.027631655	
t Critical one-tail	1.688297714	
P(T<=t) two-tail	0.05526331	
t Critical two-tail	2.028094001	

APPENDIX C

IRB AND STUDY APPROVAL DOCUMENTS

North Texas Regional Institutional Review Board
UNT Health Science Center
BOARD ACTION

IRB Project #: 2019-108 Date Submitted: New submission

Principal Investigator: Stephen Mathew, PhD with CRM student Kellyn Pollard

Project Title: Retrospective Analysis of Phase 3 Clinical Trial to Evaluate the Efficacy of Vadadustat in Anemia Secondary to Chronic Kidney Disease 7/25/19

Sponsor Protocol #: Institution: UNT Health Science Center

Department: Clinical Research Management Contact Info:

In accordance with North Texas Regional IRB policy on the protection of human subjects, the following action has been taken on the above referenced project. Approval, when given,is **only** for the project as submitted. **No changes** may be implemented without first receiving IRB review and approval. Only use the IRB approved (stamped) study material.

The Principal Investigator must notify the IRB immediately if any new potential Conflict of Interest arises or if CITI educational training lapses for any of the Key Personnel involved with the study.

☑ Project has received approval through: **July 25, 2020**

☐ Informed consent(s*) approved as submitted on:

You **MUST** use the version (s) attached rather than previously approved versions. In addition, only consent documents which bear the official North Texas Regional IRB approval stamp can be used with subjects.

*Including:

☐ Study Protocol dated _____ approved as submitted.

☐ Investigator's Brochure _____ approved as submitted.

☐ Protocol Synopsis approved as submitted on: _____

☐ Amendment _____ to the protocol approved as submitted.

☐ Progress Report/Continuing Review completed, project has received approval through: _____

☐ Project has been reviewed. In order to receive approval, you must incorporate the attached modifications. You must submit one "tracked changes" version showing the markup and one "clean" copy of the revised protocol synopsis, informed consent, and advertisements to the IRB for review. ***YOU MAY NOT BEGIN YOUR PROJECT UNTIL NOTIFIED BY THE IRB.***

☐ Project is disapproved for the reason(s) outlined (see attached).

☐ Consideration of the project has been **DEFERRED** pending resolution of the issues(s) outlined (see attached).

☐ Completion of project is acknowledged and all required paperwork has been received.

☑ Special Findings/Other

The North Texas Regional IRB acknowledges the research activity (secondary data analysis) is conducted under the oversight of the Copernicus IRB and Protocol# AKB-6548-CI-0017 (IRB #QU11-16-327). Dr. Mathew serves as the faculty advisor/contact for this CRM internship project.

Chair/Vice Chair/Designated Reviewer, Institutional Review Board

July 25, 2019
Date

Board Action (revised January 2019)

Board Action-page 2

PI: Stephen Mathew, PhD

IRB Project #: 2019-108

Date: 07/25/2019

SPECIAL FINDINGS:

☐ CHILDREN: The Board found the participation of children to be approvable under Subpart D of the federal regulations. Specifically, the research satisfies the requirements of:

☐ **45 CFR** ☐ **21 CFR**

☐ COGNITIVELY IMPAIRED: The Board found the participation of cognitively impaired subjects to be approvable under federal regulations. Specifically, the research satisfies the requirements of:

☐ **45 CFR 46.111 (b)** ☐ **21CFR 56.111 (b)**

☐ PREGNANT WOMEN or FETUSES: The Board found the participation of pregnant female subjects or fetuses to be approvable under Subpart B of federal regulations. Specifically, the research satisfies the requirements of: **45 CFR 46.204 (a) - (j)**

☐ NEONATES: The Board found the involvement of neonates to be approvable under *Subpart B* of federal regulations. Specifically, the research satisfies the requirements of: **45 CFR**

☐ PRISONERS: The Board found the participation of prisoners to be approvable under *Subpart C* of federal regulations. Specifically, the research satisfies the requirements of: **45 CFR 46.305 (a), (b) and (c)**

☐ OTHER:

OTHER

☐ **Expedited Review Procedures (under 45 CFR 46)**

Project ☐ Approved ☐ Approved for Continuation ☐ Modifications approved **under the provisions of:**

☐ **45 CFR 46.110 (b) (1) (ii)** minor changes in previously approved research during the period for which approval is authorized.

☐ **HIPAA Waiver:** The Board finds this study meets all legal requirements for a Waiver of Individual Authorization under HIPAA pursuant to 45 CFR 164.512 (i) (2) (i)-(v) and approves the request under:

☐ **Informed Consent Waiver:** The Board finds this project qualifies for a _____ under the provisions of _____

☑ **Other IRB Approved Research Documentation Includes:**

IRB acknowledges Copernicus IRB Approval Letter and Clinical Protocol

☑ **Other Comments:**

NOTE: As the original project received initial review and approval under the Pre-2018 Requirements, this project requires an annual review. Please seek an annual review of this project prior to the one year anniversary or submit a Final Report. Please note that the Final Report can be submitted prior to the one year anniversary (as soon as the project is closed).

CLINICAL PROTOCOL

PHASE 3, RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED STUDY EVALUATING THE EFFICACY AND SAFETY OF ORAL VADADUSTAT FOR THE MAINTENANCE TREATMENT OF ANEMIA IN SUBJECTS WITH DIALYSIS-DEPENDENT CHRONIC KIDNEY DISEASE (DD-CKD) (INNO$_2$VATE – CONVERSION)

Compound:	Vadadustat (AKB-6548)
Protocol Number:	AKB-6548-CI-0017
US IND Number:	102,465
EudraCT Number	2016-001360-11
Phase:	Phase 3
Status/Date:	Final, Version 1.0 / 06 May 2016
Sponsor:	Akebia Therapeutics, Inc. 245 First Street Suite 1100 Cambridge, MA 02142 United States of America

copernicus group independent review board

06Jan2017

Adeel Ijaz MD
Adeel Ijaz PLLC
4309 Ridgecrest Rd Ste 100
Greenville TX 75402

Re: Protocol #: AKB-6548-CI-0017
IRB Tracking #: QUI1-16-327

Dear Dr. Ijaz,

As your IRB of record for the above referenced study, the Copernicus Group IRB board has reviewed your submission information. Enclosed is your approval notice. Be sure to carefully maintain the original documents so that copies may be made when necessary. As Principal Investigator, you agree to uphold your responsibility to protect the rights and welfare of your subject at all times while adhering to all applicable federal regulations governing the conduct of clinical research trials.

Copernicus Group IRB reserves the right to visit your research site at any time with appropriate prior notice.

Please access the Copernicus Group IRB Investigator Guidebook, which details the IRB's expectations, procedures and contact information. The Guidebook is available at www.cgirb.com or within Connexus, our electronic document management system. Please carefully read this Guidebook and have your study staff do the same. CGIRB forms and additional information regarding the conduct of clinical trials are available on our web site: www.cgirb.com.

This submission has been reviewed under the WIRB-Copernicus Group Single Review Solution. CGIRB and WIRB have entered into a reliance agreement where WIRB will rely on CGIRB to perform protocol-level reviews. WIRB and CGIRB each continue to review their separate Principal Investigators and subsequent PI-level submissions under the single protocol review.

If you have any questions regarding the contents of this letter or your working relationship with Copernicus Group IRB, please do not hesitate to call us at 1-888-303-2224 or email us at irb@cgirb.com. To avoid delay in locating your records we ask that you refer to the IRB Tracking number located in the header of this letter.

We look forward to working with you.

Copernicus Group IRB

cc: Ms. Erin Kephart , Quintiles, Inc. (Web Portal)
Ms. Janice Royall , Quintiles, Inc. (Web Portal)
Ms. Lynda Atalese , Quintiles, Inc. (Web Portal)

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