Title of Protocol	***CARAT*: *C*anagliflozin vs. Placebo for Post B*A*riatric Patients with Pe*R*sistent Type 2 Di*A*be*T*es**	
Principal Investigator / Study Sponsor	Sangeeta Kashyap, MD	
Co-Investigators	Bartolome Burguera, MD and Philip Schauer, MD	
Mailing Address	Cleveland Clinic, 9500 Euclid Avenue. Cleveland OH 44195	
E-Mail Address	KASHYAS@ccf.org	
P.I.'s Telephone	216-445-2679	Fax: 216-445-1656
Funding Source	**Janssen Scientific Affairs, LLC (Funding and Study Product) Cleveland Clinic Investigational Drug Service (IDS) Pharmacy (Placebo)**	

PURPOSE OF PROTOCOL

Obesity is one of the greatest public health challenges of our nation and a leading risk factor for type II diabetes (DM2) development. Bariatric surgery is an effective therapeutic option for inducing marked weight loss and remission of DM2 (i.e., euglycemia without glucose lowering agents), which is supported by the publication of several randomized controlled trials (1-4). However, the variable durability of diabetes remission after surgery has been noted and is dependent on the extent of weight loss, degree of weight regain after the peak in weight loss, surgery type, and the duration of diabetes prior to surgery (5). An estimated ~20-40% of patients redevelop diabetes and require the addition of anti-diabetic agents within five years after gastric bypass despite achieving initial remission status (6-8). Consequently, there is a significant clinical need to identify evidenced based medical strategies to optimize the cardio-metabolic benefits of bariatric surgery, particularly for those with residual and/or recurrent DM2 (i.e., HbA1c $\geq$ 6.5%) post-bariatric surgery.

Preliminary evidence from our randomized control trial of gastric bypass vs. sleeve gastrectomy (SG) vs. intensive medical therapy (IMT) for diabetes (STAMPEDE) indicates that diabetes non-remission (HbA1c >6.5%) at 24 months occurs in ~ 39% of post-gastric bypass patients with an average weight regain of ~5 kg (4). Recently, we have related diabetes remission status to improvements in pancreatic ß-cell function, which is associated with greater weight/fat loss and elevations in adiponectin levels. Therefore, the aforesaid represent potential therapeutic targets with medical therapy in those who do not remit (9). Moreover, agents that act independently of insulin may be ideal for surgical non-remitters with poor residual beta cell function. For instance, canagliflozin, a novel class of antihyperglycemic agent, has been demonstrated to facilitate a favorable metabolic profile

(i.e., weight loss and reductions in blood pressure without hypoglycemia) for patients with DM2 that may be ideally suited for post bariatric patients (10,11). *Thus, the purpose of this proposal is to evaluate the efficacy of canagliflozin in the post-operative management of DM2. We hypothesize that glucose lowering strategies that act independently of insulin and facilitate weight loss, will lead to better glycemic control and produce more favorable cardiometabolic changes than standard of care approach for post bariatric patients with persistent type 2 diabetes.* Therefore, the specific aims are:

1. Determine the clinical efficacy of canagliflozin vs. placebo in patients with type 2 diabetes post-bariatric surgery.

To test the clinical efficacy of canagliflozin in post bariatric patients (i.e., adjustable gastric banding [AB], Roux-en-y gastric bypass [RYGB] and sleeve gastrectomy [SG]) with type 2 diabetes, we will perform a randomized clinical trial of post bariatric surgery (>1 year) patients (N=36) and assign them into either a 6 month intervention of a) canagliflozin monotherapy (300mg qd) (N= 24) or b) placebo (N = 12). Including AB, RYGB, and SG subjects would give a more comprehensive understanding of the effects of canagliflozin, in the post-operative setting, given that they are the most common metabolic surgeries. The primary outcome measure is the change in Hba1c from randomization until 6 months in the medication group, relative to placebo. Secondary measures include the percentage of subjects who achieve glycemic control at 6-months (i.e., Hba1c <6.5%), fasting glucose, change in body weight, lipid, blood pressure control and symptomatic hypoglycemia episodes (per AE reporting).

2. **Determine whether the cardiometabolic benefits of canagliflozin in post-bariatric individuals with diabetes is related to improvements in weight loss and adipokine (ie. adiponectin) levels.**

This is an exploratory aim to gain insight into whether canagliflozin treatment improves weight loss and adipose tissue health (i.e., lower body fat/increase adiponectin) in post bariatric patients with type 2 diabetes vs. placebo treated subjects who will continue to experience weight regain. All subjects will undergo body composition testing with DXA scans at randomization and at 6 months, along with measures of leptin and high molecular weight (HMW) adiponectin. The aim regarding adiponectin is exploratory in this protocol, but we postulate that anti-diabetic therapies that enhance weight loss post-surgery may

increase adiponectin levels and hence, adiponectin related effects to improve glucose homeostasis and cardiometabolic risk.

Data generated from this proposal will allow us to define the optimal role of canagliflozin as an adjunctive medical therapy for the treatment of recurrent diabetes and to better understand the physiological factors underlying diabetes treatment, in post metabolic surgery individuals. Once identified, successful interventions may be initiated early after bariatric surgery for select high-risk patients that may be prone to relapse, to optimize the cardiometabolic benefits of surgery for patients with obesity and DM2.

BACKGROUND / PRELIMINARY DATA FOR THE RESEARCH

Bariatric surgery is rapidly gaining approval as a treatment for severe obesity, especially when complicated by DM2. An estimated 350,000 operations per year were performed globally at a cost of over $5 billion (12). In centers of excellence, post-operative care is usually administered by the patient's endocrinologist and multi-disciplinary obesity teams and involves long-term evaluation of co-morbidity status, weight regain and multiple nutritional deficiencies. In the private sector, particularly, patients who are self-funding for surgery often do not choose to stay in follow up and high attrition rates remain a major challenge. Many observational studies and their meta-analyses have documented diabetes remission to occur in 78% of patients with morbid obesity (6,13,14). Two recent randomized control trials (2,4) document the effectiveness of gastric bypass surgery over intensive medical therapy to induce diabetes remission in the 42% range in patients with moderate obesity (BMI 30-40 kg/m2). However, long-term observational studies document a disquieting trend that a growing number of patients (25-40%) with DM2 do not achieve "biochemical remission" of hyperglycemia defined as normal glycemic control (HbA1c < 6% or <42 mmol/mol) without the need for diabetic medications (15), or are unable to sustain

this effect long-term despite initial success with weight loss (6,7,16). This proposal will target individuals who achieve early metabolic benefit, but are not able to sustain these effects long-term.

Although the definition of diabetes remission is highly variable and controversial, Buse et al. (15) proposes that partial remission of hyperglycemia consists of an HbA1c below 6.5% (48 mmol/mol) without the need for diabetes medications and non-remission status as HbA1c > 7% (53 mmol/mol) with or without the need for medications. According to the remission definition criteria proposed by Buse et al. (15) complete remission rates for diabetes at 23 months in a retrospective review of 1006 patients undergoing bariatric surgery was 34.4% overall (17). In another series of 177 super-obese patients with diabetes, 43% of patients who initially underwent diabetes remission after gastric bypass redeveloped diabetes (7). Sjostrom et al. (18) reported an improvement in the rate of recovery from diabetes at 2 and 10 years following bariatric surgery vs. conventional medical treatment in the Swedish Obesity Study (SOS) cohort. However the rate of recovery from diabetes dropped from 72% at 2 years to 36% at 10 years following surgery, implying a ~50% relapse rate for diabetes recovery. Although the relapse rates for diabetes control following various procedures are merely estimates, given the lack of adequate follow-up in observational reports, little information regarding long-term management of diabetes following bariatric surgery is available.

Schauer et al. (14), looking specifically at the effects of RYGB on DM2, reported that patients with the shortest duration (5 years) of diabetes, its mildest form (diet-controlled) and the greatest weight loss after surgery were those most likely to achieve complete resolution of their diabetes. Pre-operative glycemic control also impacted the rate of DM2 resolution. They

pointed out that patients with the more severe forms of DM2 according to duration and insulin use showed significantly less weight loss than those who had milder forms. The study of 191 patients after 5 years of follow up indicated that 65% treated by oral agents and 27% treated by insulin achieved an euglycemic status eliminating the requirement for anti-diabetic medications. The team also observed that DM2 patients had an overall lower excess weight loss than non-diabetic patients, as did Dixon et al.(1), who investigated the use of gastric banding. In the Schauer et al. study (14), excess weight loss was significantly lower in patients using oral agents or insulin vs. those with impaired fasting glucose and on a diet only: 57% and 59% vs. 73% and 65%, respectively. Also postoperative HbA1c levels in patients using insulin were significantly higher than in patients with impaired fasting: 6.0% vs. 5.0%, respectively ($p < 0.001$).

Re-emergence of Diabetes Following Bariatric Surgery; Clinical Considerations

Possible factors associated with diabetes non-remission based on observational clinical studies consist of older age, male gender, lower pre-operative BMI, surgery type (restrictive vs. bypass), diabetes duration >10 years, insulin use pre-operatively, inadequate weight loss/weight regain, severity of pre-operative beta cell dysfunction. Non-remission or re-emergence of diabetes following gastric bypass and restrictive procedures particularly is increasingly recognized, and although studies examining the mechanistic links are lacking, clinical observations suggest that inadequate weight loss and weight regain to be a factor for sub-optimal control of diabetes following these procedures (19,20). Previous studies highlight that despite success with weight loss post-gastric bypass surgery, many patients remain in the obese BMI category (>30 kg/m2) following surgery. Sub-optimal weight loss and weight regain has been associated with noncompliance with dietary and lifestyle recommendations,

variations in pre-surgical weight loss, and, occasionally, surgical failure that are often associated with psychosocial stressors (21). Prevention of weight gain requires optimizing patient selection criteria, consideration of benefits of bypass vs. banding or SG procedures, and adherence to scheduled visits. Psychological factors such as uncontrolled depression, eating disorders and previous history of sexual abuse has also been linked to weight regain and inadequate weight loss and warrant evaluation and continuing treatment (22). Post-surgical adherence to scheduled visits and compliance is also a major factor related to success of weight loss maintenance (20). The factors associated with re-development of DM2 following gastric bypass are related to poor baseline beta cell function in patients characterized by advanced duration (i.e., insulin requiring) and severity of DM2 (i.e., hyperglycemia) in older aged individuals (7,14). The incidence of residual or worsening DM2 following RYGB in one small study of 42 DM2 subjects was noted to be 26% 3 years following surgery and was associated with a lower pre-operative body mass index (BMI) (23). Although much of the literature has focused on biochemical remission following bariatric surgery, little information about the effects of surgery on long-term diabetes complications exist. The importance of on-going and continuous surveillance for micro-vascular complications in post-surgical patients is also warranted and will be addressed to some extent in this study.

Diabetes Therapies for Recurrent Diabetes Following Bariatric Surgery

Non-remission of hyperglycemia is noted by HbA1c $\geq$ 6.5% and necessitate the use of diet and exercise counseling followed by the use of anti-diabetic medications. Initial preoperative assessment of DM2 should include documentation of type 1, latent onset autoimmune diabetes (LADA), or DM2 given the increasing prevalence of obesity in all

classifications of diabetes. The determination of C-peptide and autoimmune status is helpful in particular clinical scenarios where a primary ß cell defect is suspected. Indicators of diabetes severity and poor residual pancreatic ß cell function include duration of disease > 10 years, use of insulin, poor glycemic control despite oral agents, and presence of microvascular complications. Diabetes non-remission following gastric bypass procedures needs to be considered in the setting of inadequate weight loss or weight regain and progressive beta cell failure without weight regain. The treatment of diabetes following gastric bypass should ideally target glycemic control and weight loss with agents that induce weight loss. Metformin remains the first line agent for DM2 in that it improves insulin sensitivity by suppressing hepatic gluconeogenesis and increases muscle/liver glucose uptake by increasing AMPK activity. A recent report indicated accelerated absorption and bioavailability of metformin following gastric bypass and indicated that a reduction in dosage may be required for achieving glycemic control (24). Metformin however is associated with significant gastrointestinal side effects that may be further exacerbated in post gastric bypass population. Sulfonylureas (SFU) improve insulin secretion and in the early post-operative period following bariatric surgery may precipitate hypoglycemia and precipitate dumping symptoms. Furthermore, SFUs are associated with exacerbating ß-cell exhaustion (25). Therefore, caution is warranted for the use of these agents. For those patients who do not respond to SFU, insulin therapy is indicated with the introduction of basal insulin following by the addition of prandial insulin as indicated by the level of glycemic control. Insulin therapy is effective in lowering glucose levels and reduces glucotoxicity, lipotoxicity and inflammatory effects related to ß-cell failure and is known to rest ß-cell function (26,27). Well recognized adverse effects of insulin therapy include the incidence of hypoglycemia and

weight regain that could counteract the beneficial effects of gastric bypass for diabetes and weight management in bariatric populations. Moreover, multiple daily injections are burdensome to patients and lead to non-adherence. Given the adverse effects of the aforementioned pharmacological agents, our strategy in this study is to determine the clinical efficacy of sodium glucose transport inhibitor, canagliflozin monotherapy vs. placebo on clinical and metabolic outcomes in patients post bariatric surgery.

Clinical application of recently FDA approved sodium glucose transport inhibitors, i.e., canagliflozin, to optimize benefits of bariatric surgery for weight and glycemic control seems highly attractive and logical, but experimental evidence for their use is currently lacking for the bariatric population. Clinical trials in DM2 have demonstrated favorable effects to lower glucose levels, weight and blood pressure and these benefits may benefit post bariatric patients with persistent metabolic syndrome features.

Significance and Innovation:

With the marked increase in bariatric procedures being performed in this country for severe obesity and obesity related diabetes (over 200,000/year), monitoring for recurrent DM2 and its complications is crucial. However, guidelines for post-surgical diabetes management are not evidence based. There are currently no studies evaluating the efficacy, safety and mechanisms of action of various adjunctive medical approaches to optimize the metabolic benefits of gastric bypass surgery. Moreover, no studies have simultaneously determined the effects of various glucose lowering approaches on glucose homeostasis, body weight and adipose tissue regulation. This study will be highly informative and will provide insight to the medical community on the clinical efficacy and benefits of canagliflozin to manage diabetes post gastric bypass surgery. Once identified, these interventions may be initiated early after

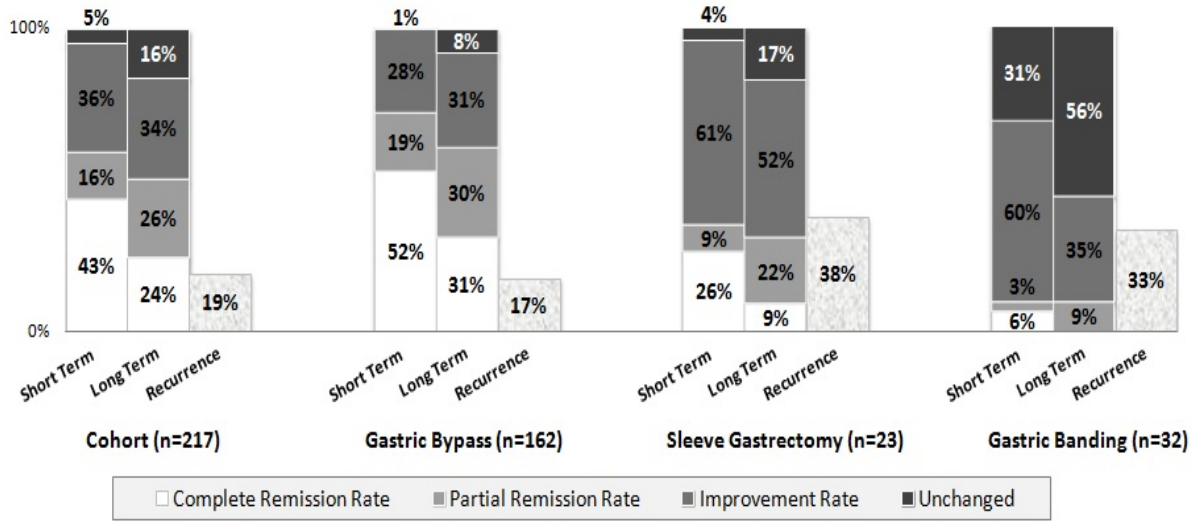
bariatric surgery or before non-remission occurs for select high risk patients to optimize benefits of metabolic surgery.

Our bariatric surgical program is a Center for Excellence and a high volume provider of gastric bypass procedures for patients with medical indications with follow up care provided by endocrinologists and a multidisciplinary obesity team. This program provides an ideal environment in which to pursue novel and innovative approaches that couples medical care delivery with research that is both clinically significant and scientifically meaningful using a novel and innovative approach.

PRELIMINARY DATA:

1. Diabetes remission/non-remission rates following bariatric surgery from Cleveland Clinic observational study (***Annals of Surgery, 6/2013 epub. Brethauer S et al.***)

N= 217 consecutive subjects with type 2 diabetes of median 6yr duration, Hba1c of 7.5%, BMI of 50 kg/m2, age 49 yrs. N= 162 following gastric bypass with complete diabetes remission (HbA1c <6%) of 31%; diabetes non-remission of 69% and diabetes recurrence rate of 17% during 6 year median follow up. Predictors of remission: weight loss (P 0.006), short diabetes duration (P =<0.001) and bypass vs. banding procedure (P = 0.02).



2. Diabetes remission/non-remission rates and weight regain in on-going STAMPEDE trial follow up at 24 months:

Subjects with type 2 diabetes in STAMPEDE trial N= 150 randomized to medical therapy (N= 50) vs. Roux-n-Y gastric bypass (n = 50) or SG (N = 50) ; baseline age 48 yrs., diabetes duration 8 years, BMI 36 kg/m2, HbA1c of 9%.

	Gastric Bypass	Sleeve Gastrectomy
Rate of HbA1c > 6.5%-12 months	16/48 (33.3%)	22/48 (45%)
Rate of Hba1c > 6.5%-24 months	14/36 (38.9%)	14/36 (38.9%)
Rate of HbA1c > 6.5%-36 months	12/23 (52.2%)	12/23(52%)
Weight regain-24 months	30/36 (83%)	32/38 (84%)

Weight increase from nadir 24 months (Kg)	5 ± 3.9	4.9 ± 4
Weight increase from nadir 36 months (Kg)	7.6± 5	10.3 ± 11

Diabetes non-remission defined by HbA1c ≥ 6.5% increased following both surgery types (especially the SG procedure) at 24 and 36 months follow up along with weight regain from nadir weight following both procedures. These data are accumulating and unpublished since the trial is on-going for collection of follow up data. Initial primary endpoint of diabetes remission rate (HbA1c ≤6% of 42% after gastric bypass) reported in ***NEJM, April 2012 (Schauer, Kashyap, Wolski et al.)***.

3. Metabolic Determinants of HbA1c ≤ 6.5% at 24 months in subset (N= 60) of medical and surgical patients enrolled in STAMPEDE trial:

A multivariate logistic model of metabolic parameters that associated with HbA1c ≤ 6.5% at 24 months in the substudy cohort of 54 subjects that underwent medical, RYGB, and SG intervention arms combined demonstrated that the fold increase in the oral disposition index (ß cell function) was associated with an increased OR of 1.67, and the increase in abdominal fat was associated with a lower OR of 0.878 to achieve glycemic control at 24 months. ***(Kashyap et al. Diabetes Care; Feb 24, 2013 epub).*** This suggests that improved ß cell function and reduction of abdominal fat are key metabolic determinants of remission vs. non-remission status in medical and surgical subjects.

4. Poor Improvement in Adiponectin Levels and Inadequate Fat/Weight Loss Depict Surgical Non-remission at 24 months in STAMPEDE:

The 37(BMI: 36±3kg/m2, Age: 48±9y, HbA1c: 9.7±2%) DM2 post-bariatric (RYGB and SG) surgery subjects who underwent RYGB and SG were analyzed based on remission vs. non-remission status defined by HbA1c of < 6.5% or > 6.5% and/or hypoglycemic medications. Bariatric surgery-induced 45% and 38% DM2remission rates at 12 and 24m, respectively, with RYGB yielding higher remission rates than SG at 24m (P<0.05). (Data submitted to ADA 2014 Scientific Sessions). As shown in the table, surgical remitters had greater weight loss, total body fat loss, rises in adiponectin levels and higher levels of GLP-1 stimulation with meal intake.

Variables at 24 months	Remission (HbA1c <6.5%	Non-remission (HbA1c>6.5%)	P-value
BMI (kg/m2)change	-9.97 (-10.6, -7.9)	-6.8 (-9, -6.06)	0.03
Body fat % change	-11.1(-14.6,-7.8)	-7.4(-10,-4.6)	0.04
Adiponectin ng/ml change	2.9 (1.7, 4.4)	-0.1 (-2.2, 0.9)	0.003
Truncal fat % change	-13.8 (-21.5, -10)	-10 (-13, -5.7)	0.04
Change in Disposition Index	0.31	0.06	<0.001

Baseline adiponectin predicted lower HbA1c at 12 and 24m (R=0.34, P=0.04 and R=0.33, P=0.04). Elevated adiponectin correlated with enhanced ß-cell function at 12 (R=0.33, P=0.04) and 24m (R=0.47, P<0.01) as well as weight loss at 24m (R=-0.32, P=0.05). Thus, poor fat loss and blunted rises in adiponectin depict DM2 non-remission 2 years after bariatric surgery.

5. Observational data on the use of generic phentermine and topirimate on residual diabetes in

post-bariatric subjects enrolled in STAMPEDE trial: In forty subjects with residual type 2 diabetes (age 50yrs, HbA1c 8.2%, BMI 32 kg/m2) 32 months following gastric bypass and SG, 3 month use of generic phentermine (15mg) resulted in a decrease in HbA1c (8.4 ± 1.3 to 6.8 ± 0.8, P <0.05)) and body weight by a median of 6.5kg. The use of basal insulin (0.3u/kg/day) resulted in less of a decrease in Hba1c (8.1±1.4 to 7.3%±0.5) and a median weight gain of 1.5kg.

Summary of Preliminary Data

These preliminary data from our institution demonstrate that relapse of diabetes control does occur with increasing time of follow up from gastric bypass procedure. Additionally, weight regain from nadir weight loss achieved after gastric bypass increases with time of follow up from surgery. Moreover, inadequate weight/fat loss and poor rise of adiponectin depict surgical non-remitters and these factors might be targeted with medical therapies to enhance greater weight/fat loss and increase adipose tissue health.

DESCRIPTION OF THE RESEARCH PROTOCOL

Experimental Plan: This is a prospective, randomized, double-blinded clinical trial for patients with recurrent type 2 diabetes post-gastric bypass surgery that will compare a 6 month course of canagliflozin monotherapy vs. placebo on clinical outcomes of type 2 diabetes. The rationale for including those subjects that initially remit but later redevelop as opposed to those that never achieve remission following metabolic surgery is based on several factors. Those that never achieve remission following metabolic surgery may not have had type 2 diabetes (but rather be autoimmune or MODY) prior to surgery or have the

ability to generate insulin from very poor residual ß-cell function. Alternatively, those that initially remit have the potential to achieve durable remission in the future and may likely respond to adjunctive medical therapy. RYGB, AB, and SG operations comprise the majority of the bariatric practice and approximately 20-40% of those that initially remit may re-develop diabetes within a 5 year timeframe. Following consent and a screening visit to assess eligibility and clinical status (i.e. historical, physical and biochemical parameters including glycemic control and a pregnancy test in females), a baseline visit with diabetes educator will take place to provide standard diabetes education, nutrition and exercise prescription.

Sample Size Considerations

Comparisons of the primary endpoint, change in HbbA1c levels from randomization, between canagliflozin and placebo groups will be performed using analysis of covariance models. Since the correlation between baseline levels of HbA1c and change in the measure at 6 months is not presently well known, power calculations are based on use of two-sample t-tests, which assume similarity of the two randomized groups on HbA1c at baseline. Enrollment of 36 patients is planned. Assuming use of a two-sided t-tests with a significance level of 0.05, and that variability in HbA1c change at 6 months is similar to that seen at 1 year in Cefalu et al. (2013) [SD=0.9%], there will be 80% power to detect mean differences of 1.0% in HbA1c change between groups with enrollment of 22 patients in the canagliflozin group and 11 in the placebo group. Power calculations were performed using SAS software (Version 9.4; Cary, NC). If we assume dropout of 10%, and enroll 24 patients in the canagliflozin group and 12 in the placebo group, this should allow for adequate power despite the expected loss to follow-up. Since analysis of covariance models will provide increased

power relative to t-tests in the presence of positive correlation (Borm et al, 2007), the effect size that can be detected is conservatively large.

Nutritional assessment for vitamin/mineral deficiency will be performed per clinical care guidelines(46) at the screening visit. Subjects will be asked to take nutritional supplements (i.e. vitamins and minerals) per current clinical guidelines for post-bariatric patients. Stable doses of supplements will be established for at least 2 weeks prior to randomization. Thirty-six subjects with recurrent diabetes that are naïve to hypoglycemic agents with HbA1c greater than or equal to 6.5% and less than 11% will be randomly assigned to a six month course of a) canagliflozin 100mg for 2 weeks titrated up to 300 mg daily (N = 24) vs. placebo (n= 12) at the randomization. Patients taking an anti-diabetic medication will be asked to washout for 8 weeks prior to the randomization visit. At randomization, biochemical assessment of glycemic parameters (fasting glucose, HbA1c), lipid panel, complete metabolic panel, uric acid, leptin, total and HMW adiponectin, C-reactive protein and urine for albumin/creatinine ratio will be performed. DXA scan will be performed for body fat composition.

Following randomization, subjects will be clinically evaluated at three office visits at 6 weeks, 3 and 6 months by PI and/or the research staff. The primary outcome measures at 6 months post-randomization include HbA1c followed by the change in HbA1c from randomization. Secondary measures include fasting glucose, BMI, change in body weight, blood pressure, lipid profile. Symptomatic hypoglycemia (blood glucose < 70) and drug related side effects (i.e. mycotic genital infections, urinary tract infection) will be monitored with adverse event reporting. Metabolic testing in all subjects at randomization and at 6

months will include a DXA scan for body fat composition and blood for leptin and adiponectin levels.

Rescue glucose lowering therapy will be provided for all subjects with a blood glucose >250 mg/dl. If chronic uncontrolled hyperglycemia (HbA1c >11%) occurs then basal bolus insulin will be implemented. Subjects (20-75 years) who underwent AB, SG or RYGB within the past 15-years will be recruited. Including subjects who underwent surgery within the past 15-years will broaden the subject pool, as additional subjects who initially remitted and were subsequently rediagnosed will be identified. However, we will prioritize subjects who underwent metabolic surgery ≤6 years ago and who initially achieved remission status documented by Hba1c of ≤6.5% within first year and a subsequent glycated hemoglobin ≥ 7.5% (without any hypoglycemic agents) and less than 11% as upper limit. The rationale to prioritize patients that initially remit is that these patients have demonstrated ability to respond to surgical weight loss and subsequently redeveloped the disease. Whereas those that never achieved initial remission status may not respond to any intervention due to inexorable beta cell failure.

Initial recruitment will be achieved by a general awareness campaign, which will emphasize a study of methods of diabetes management post metabolic surgery. All patients will be pre-screened for inclusion and exclusion criteria by our clinical trial research nurse coordinator and/or research fellow. Evaluation of the inclusion and exclusion criteria, which are listed below, will occur both at the initial screening visit and the baseline visit, prior to randomization.

Statistical Methods

The primary analysis will be performed using a modified intent to treat analysis which includes all patients receiving at least one dose of the drug they were assigned. A secondary, per-protocol analysis may also be performed using those demonstrating compliance to their assigned treatment throughout the study. All endpoints will be evaluated using a significance level of 0.05, and no correction for multiple testing is planned.

To evaluate changes in HbA1c and other continuous endpoints at 6 months, analysis of covariance models will be fit. In these models, change from baseline will be the outcome, group membership will be the predictor of interest, and baseline level of the outcome will be a covariate. If distributional assumptions of the model are not met, transformation of the outcome measure will be considered to improve model fit, as will the use of alternative rank-based approaches. Estimated changes and differences in the changes at 6 months between groups will be presented with 95% confidence intervals. Categorical factors will be presented using frequencies and percentages, and comparisons of these measures between groups will be performed using Pearson chi-square tests or Fisher exact tests, as appropriate. Continuous patient characteristics will be summarized using means and standard deviations or medians and quartiles, depending on their distribution.

Inclusion Criteria:

1. Post-AB, RYGB, and SG patients who underwent surgery >1 and <15 years ago, in the Cleveland surrounding area
2. 20-75 years of age

3. DM2 diagnosis (history, medication usage, biochemical criteria) prior to and after surgery; after surgery, defined by a single HbA1c of greater or equal to 6.5% at consent and screening.

4. Metformin patients must have an HbA1c greater than or equal to 6.5% but less than or equal to 11% at randomization; for diet controlled patients (i.e. not on any T2D medication), HbA1c must be greater than or equal to 6.5% at randomization.

5. Patient reporting of improvement in T2D status or objective improvements in T2D status at any time post-surgery.

6. eGFR ≥ 60mL/min prior to randomization

7. Has the ability and willingness to provide informed consent.

8. Is able to understand the options and to comply with the requirements of each program.

9. Female subject agrees to have a serum pregnancy test at screening. A negative serum pregnancy test result is required prior to randomization.

10. Female patients must agree to use a reliable method of contraception for 6 months or duration of intervention.

11. Excluding research-related insulin use, patients taking an anti-diabetic medication, except insulin, are eligible and must agree to washout for 8 weeks prior to the randomization visit.

<u>Exclusion Criteria:</u>

1. Type 1 diabetes indicated by history of diabetic ketoacidosis and lack of remission in response to bariatric surgery.

2. Other post bariatric procedures (banding, duodenal switch, biliopancreatic diversion)
3. Non-research-related insulin use that is prescribed by the patient's primary care physician or endocrinologist
4. End organ diabetic complications (renal failure, cardiomyopathy, severe neuropathy/foot ulcers)
5. Documented severe or unstable depression/anxiety or eating disorder that would not enable patient to adhere to anti-diabetic treatment.
6. Clinical contraindications to use canagliflozin, i.e., history of bladder cancer, Child-Pugh class C.

In addition to a urine sample, a maximum of 60-cc of blood may be needed at each visit; 30-cc will be stored as a biorepository, for future purposes. The biorepository will be performed at randomization and at the 6 month visit. The research repository collection will be part of the protocol. The identity of the subject will be confidential as the samples will be deidentified. Specimens will be processed and stored in Preventive Research Laboratory at Cleveland Clinic. Access to these specimens will be limited to the designated PRL laboratory personnel and utilized at the discretion of the Principal Investigator.

Schedule of visits summarized:

Visit 1: Consent and Screening Visit: An assessment of clinical status for eligibility will be performed. Review of past medical history and medication usage will be reviewed. Venipuncture for HbA1c and a pregnancy test (females only). Labs for nutritional status

including B12 and 25 hydroxy vitamin D will be performed. Nutritional deficiencies will be addressed per current clinical guidelines for post-bariatric patients.

Visit 2: Baseline Visit: 45 minute visit with diabetes educator for diet/exercise prescription and glucose monitoring based on ADA clinical care guidelines.

Visit 3: Randomization visit with research coordinator and PI: Review of eligibility. Labs will be drawn for HbA1c, fasting glucose, lipid panel, uric acid, complete metabolic panel and adipokines (C-reactive protein, leptin, total and HMW adiponectin, leptin). Urine for albumin/creatinine ratio. DXA scan will be performed for body composition at this visit. Blood and urine will be collected for the bio-repository collection and is optional.

Visit 4: 6 week f/u visit: Research fellow/coordinator to assess adherence and safety.

Visit 5: 3 month visit with research coordinator and PI: Review of clinical status and biochemical labs will be drawn. These will include HbA1c and a complete metabolic panel.

Visit 6: 6 month visit with research coordinator and PI: Review of clinical status and biochemical labs will be drawn. These include HbA1c, fasting glucose, lipid panel, uric acid, complete metabolic panel and uric acid. Urine for albumin/creatinine ratio. Additionally, a DXA scan for body composition and blood for adipokines (C-reactive protein, total and HMW adiponectin, leptin) will be performed. Blood and urine will be collected for the bio-repository collection and is optional.

The window for all visits will be +/- 4 weeks.

Research Team: Dr. Sangeeta Kashyap is the principal investigator of this study and will consult with Dr. Philip Schauer (bariatric surgeon) for enrollment of appropriate candidates who underwent metabolic surgery at any Cleveland Clinic location, but that live within two hours of the Cleveland Clinic Main Campus. Both investigators have a long standing,

productive relationship. Statistical analysis will be provided by a Cleveland Clinic Quantitative Health Sciences statistician dedicated to endocrine and diabetes research. This team is well qualified to run post-bariatric trials and have successfully run two randomized control trial of bariatric vs. medical therapy for type 2 diabetes in obese patients.

POSSIBLE RISKS

Risks associated with Canagliflozin Include:

All drugs can cause unwanted effects called side effects. As of 28 September 2015 approximately 13173 subjects have received canagliflozin in completed or ongoing studies of 12 weeks or longer.

Side effects found in these studies that are more likely to occur with canagliflozin include those below. You should speak with your doctor about any changes to your diet or other medications you are taking:

- **Dizziness or lightheadedness upon standing** - These adverse events, from a decrease in blood pressure, occur soon after starting canagliflozin and are more likely to occur in people on medicines to lower blood pressure including diuretics (water pills such as Lasix/furosemide), on a low salt diet, older patients or those who have reduced kidney function. While you are taking canagliflozin, you should try to avoid becoming dehydrated and should speak to your doctor about any changes in your diet or other medications. This side effect may occur in up to 1 in 20 people on canagliflozin, or slightly more frequently in those at risk as described above.

- **Hypoglycemia in patients taking other medications associated with hypoglycemia**

  If you take canagliflozin with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonylurea medicine or insulin may need to be lowered while you take canagliflozin and you should speak to your doctor about any changes in your other medications. This side effect is very common and may occur in more than 1 in 10 people on canagliflozin Signs and symptoms of low blood sugar may include: headache, drowsiness, weakness, dizziness, confusion, irritability, hunger, fast heart-beat, sweating, shaking or feeling jitter.

- **Increased urination and thirst** – Symptoms might include feeling thirsty , having a dry tongue, urinating more frequently or in larger amounts, an urgent need to urinate or more frequent urination at night. These side effects may occur in up to 1 in 20 people taking canagliflozin.
- **Urinary tract infections** – Symptoms of urinary tract infections may include burning with urination, discomfort in passing urine, or fever. This side effect may occur in up to 1 in 20 people on canagliflozin.
- **Allergic reaction including rash or hives** – These events can occur shortly after starting canagliflozin, are generally not serious or associated with other serious symptoms, such as breathing problems. This side effect may occur in up to 1 in 20 people on canagliflozin.
- **Constipation** – The side effect of constipation may occur in slightly more than 1 in 50 people on canagliflozin.
- **Nausea -** There is a slightly higher rate of nausea (stomach sickness or queasy sensation) with canagliflozin. . The side effect of nausea may occur in slightly more than 1 in 50 people on canagliflozin.

  For Women:

- Vaginal yeast infections and vaginal itching. You may have symptoms such as vaginal itching, burning, irritation, odor or discharge. This side effect may occur in slightly more than 1 in 10 women on canagliflozin.

  For Men:

- Yeast infection at the head of the penis. You may have symptoms such as penile itching, irritation, burning, swelling, foul smelling discharge or pain. In 0.3% (1 in 300) of men who are not circumcised, this could lead to swelling of the foreskin, and require circumcision. The side effect of yeast infection may occur in up to 1 in 20 men on canagliflozin. Laboratory changes that have been observed in clinical studies with canagliflozin include:
    - An increase in the LDL cholesterol
    - An increase in serum potassium, phosphate and/or hemoglobin; decreases in serum urate can also occur. These changes are generally not serious and not associated with serious symptoms.
    - A change in lab tests associated with kidney function might occur. These changes have generally been temporary and may relate to hydration status.
- **Diabetic ketoacidosis** - your blood may show increased levels of blood acids called ketones. Sometimes this can occur even if your blood sugar levels are not very high (e.g.,

less than 250 mg/dL [13.9 mmol/L]). The risk of developing diabetic ketoacidosis may be increased with prolonged fasting, excessive alcohol consumption, dehydration, sudden reductions in insulin dose, or a higher need of insulin due to major surgery or serious illness. Symptoms may include difficulty breathing, nausea, vomiting, excessive thirst, rapid weight loss, a sweet or metallic taste in your mouth, a different odor to your urine or sweat, abdominal pain, confusion, fruity-smelling breath, and unusual fatigue or sleepiness. This side effect may occur in up to 1 in 1000 people with Type 2 diabetes. Call your doctor if you experience these symptoms. Do not stop or change study drug or diabetes medicines without first discussing with your doctor.

- **Bone fractures** - may occur in up to 1 in 50 people per year on canagliflozin. Clinical trials confirm the finding that fractures occur more frequently with canagliflozin than placebo, which is an inactive treatment. Fractures can occur as early as 12 weeks after starting the drug.
- **Amputation** of the toes (and to a lesser extent the foot or leg) could occur in up to 1 in 150 people per year on canagliflozin. This risk is greater in those with a prior history of amputation, disease of the circulation involving the legs or in those with nerve damage due to diabetes.
- **Decreased bone mineral density** - A clinical trial showed that canagliflozin caused greater loss of bone mineral density at the hip and lower spine than placebo.

Side effects in patients not involved in clinical studies who have been prescribed canagliflozin to treat their diabetes include those below. It is difficult to know specifically how often these side effects occur or always be certain if they are more likely to occur as a result of canagliflozin because these were not reported in the manner similar to data collection in a clinical study.

- Serious allergic reactions, including those with the symptoms of swelling of the face, throat, and/or tongue or breathing problems.

- Related to changes in lab tests associated with kidney function, severe cases of decreases in kidney function have been reported more commonly in patients who were dehydrated. Only subjects with an eGFR $\geq$ 60mL/min will be enrolled into this study. While participating in this study, if a subject's lab results indicate a decline in eGFR between 45-60mL/min, the daily dose of canagliflozin will not exceed 100mg. If a subject's lab results indicate a decline in eGFR to <45mL/min, study medication will be withdrawn.

- Infections of the urinary tract that can spread to the kidneys or into the bloodstream.

Canagliflozin has been tested for its ability to cause harm to the fetus during pregnancy or cause birth defects. These studies have been done in animals. The studies that have been completed do not indicate that canagliflozin is associated with birth defects.
Nonetheless, women who are pregnant, lactating or intend to become pregnant during the study will be not allowed to participate in the study. Women who could possibly become pregnant

must have a negative pregnancy test prior to starting on the study drug and report immediately to the study site if they suspect they are pregnant during the study.

If you are able to have children and you are heterosexually active, you must use birth control (contraception) during the study. Birth control methods that can be used while in this study include: avoiding sex, birth control pills, birth control injections or patch, intrauterine device, barrier method (for example, condoms or diaphragm) combined with spermicide (foam, cream, or gel), or your male partner is sterile (e.g. sperm tubes are cut or blocked). The type of birth control you use must be discussed with the study doctor before you begin the study. The study doctor must approve the method you use before you can enter the study.

If you become pregnant during the study, you must tell the doctor immediately. You will have to stop taking the study drug. The doctor will advise you about your medical care and will ask you to allow him/her to collect information about your pregnancy and the health of your baby.

For male subjects, if your partner becomes pregnant, you must tell the study doctor immediately.

Adverse event reporting:

I. Management of Safety Data

This Study has been designated as an interventional study. Janssen requirements for IIS interventional studies are all adverse events regardless of causality and special situations excluding those from subjects not exposed to a Janssen Medicinal Product and product quality complaints with or without an adverse event will be reported, once the subject has signed and dated an Informed Consent Form is obtained until the subject has completed participation in the study and for 30 days after the last dose of study drug.

II. Definitions

a. Adverse Event (AE)

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non- investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH]).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

b. Adverse Events of Special Interest

Events that Janssen Scientific Affairs is actively monitoring as a result of a previously identified signal (even if non-serious). These adverse events are: Hypoglycemia, increased urination and

thirst, urinary tract infections, allergic reaction including rash or hives, constipation, nausea, changes in blood work. For women-vaginal yeast infections and vaginal itching. For men-yeast infection at the head of the penis.

c. Individual Case Safety Report (ICSR)

A valid ICSR must contain the four minimum criteria required to meet regulatory reporting requirements.

- an identifiable subject (not disclosing the subject's name and address)
- an identifiable reporter (investigational site)
- a Janssen medicinal product
- an adverse event, outcome, or certain special situation

The minimum information required is:

- suspected Janssen product (doses, indication)
- date of therapy (start and end date, if available)
- batch or lot number, if available
- subject details (subject ID and country)
- gender
- age at AE onset
- reporter ID
- adverse event detail (AE verbatim in English), onset date, relatedness, causality, action taken, outcome, (if available)
- Janssen protocol ID

d. Product Quality Complaint (PQC)

A product quality compliant is related to a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product, or delivery system. Not all PQCs involve a subject. Lot and batch numbers are of high significance and need to be collected whenever available.

Examples of PQC include but not limited to:

- Functional Problem: e.g., altered delivery rate in a controlled release product
- Physical Defect: e.g. abnormal odor, broken or crushed tablets/capsules
- Potential Dosing Device Malfunction: e.g., autoinjector button not working, needle detaching from syringe
- Suspected Contamination
- Suspected Counterfeit.

e. Serious Adverse Event (SAE)

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening

(The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is medically important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

NOTE: DEATH FOR ANY REASON SHOULD BE REPORTED AS A SERIOUS ADVERSE EVENT.

For reports of hospitalization, it is the sign, symptom or diagnosis which led to the hospitalization that is the serious event for which details must be provided.

Any event requiring in-patient hospital admission (or the prolongation of hospitalization) must be reported as an SAE. Events that do not meet the criteria for SAE reporting are:
- Reasons described in the Protocol, e.g. drug administration, Protocol-required testing
- Social reasons, e.g. overnight stay because of distance between home and hospital
- Surgery or procedure planned and documented prior to entry into the Study.

Any event requiring hospitalization or prolongation of hospitalization that occurs during the study must be reported as a serious adverse event, except hospitalizations for the following:
- Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study. [Note: Hospitalizations that were planned before the start of data collection and where the underlying condition for which the hospitalization was planned has not worsened will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.]

The cause of death of a subject in a study within 30 days of the last dose of study drug, whether or not the event is expected or associated with the study drug, is considered a serious adverse event.

f. Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For a medicinal product(s) with a

marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the applicable product information.

III. Special Situations

Safety events of interest for a Janssen medicinal product that require expediting reporting and/or safety evaluation include, but are not limited to:

- Drug exposure during pregnancy (maternal and paternal)
- Overdose of a Janssen medicinal product
- Exposure to a Janssen medicinal product from breastfeeding
- Suspected abuse/misuse of a Janssen medicinal product
- Inadvertent or accidental exposure to a Janssen medicinal product
- Any failure of expected pharmacological action (i.e., lack of effect) of a Janssen medicinal product
- Medication error involving a Janssen medicinal product (with or without patient exposure to the Janssen medicinal product, e.g., name confusion)
- Suspected transmission of any infectious agent via a medicinal
- Unexpected therapeutic or clinical benefit from use of a Janssen medicinal product

These safety events may not meet the definition of an adverse event; however, they are treated in the same manner as adverse events. Special situations should be recorded on the Adverse Event page of the CRF.

Any special situation that meets the criteria of a serious adverse event should be recorded on a Serious Adverse Event Report Form and be reported to Janssen Scientific Affairs **within 24 hours of becoming aware of the event.**

IV. Management of Hyperglycemic Events

A sliding scale will be implemented for the management of hyperglycemia in the placebo or canagliflozin treated groups and during the anti-diabetic medication washout period if a subject develops random blood sugars >250 mg/dl. Subjects will use the following sliding scale:

Sliding scale with human regular insulin:
0-250: 0 units
251-300- 6 units
301-350- 8 units
351-400- 10 units.

If chronic uncontrolled hyperglycemia occurs (HbA1c > 11%) in the placebo or canagliflozin treated group then basal bolus insulin will be implemented. Basal bolus insulin will be initiated based on body weight calculation 0.5 U/kg/day with 50% of the dose given with long-acting insulins (NPH, glargine) and the remaining dose with meal insulin with rapid acting insulin (Regular, Humalog, Novolog, Apridra etc.).

V. Management of Hypoglycemic Events

The management of hypoglycemia defined as blood glucose <70 mg/dl with symptoms or requiring assistance will be implemented with oral glucose tablets or juice. The use of canagliflozin alone is typically not associated with hypoglycemia.

VI. Pregnancy

All initial reports of pregnancy must be reported to Janssen Scientific Affairs by the Sponsor Investigator **within 24 hours of their awareness of the event** using the Serious Adverse Event Form. Abnormal pregnancy outcomes (e.g. spontaneous abortion, stillbirth, and congenital anomaly) are considered serious adverse events and must be reported using the Serious Adverse Event Form.

Any subject who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study treatment.

Because the effect of the Janssen medicinal product on sperm is unknown, pregnancies in partners of male subjects exposed to a Janssen medicinal product will be reported by the Sponsor Investigator **within 24 hours of their awareness of the event** using the Serious Adverse Event Form. Depending on local legislation this may require prior consent of the partner.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

VII. Reporting Procedures for Adverse Events and Pregnancies [and/or Pregnancies in Partners]

All adverse events, whether serious or non-serious, related or not related, special situations, pregnancy exposures and/or pregnancies in partners following exposure to a Janssen medicinal product are to be documented by the investigator and recorded in the CRF and in the subject's source records. Investigators must record in the CRF their opinion concerning the relationship of the adverse event to a Janssen medicinal product.

All (serious and non-serious) adverse events reported for a Janssen medicinal product should be followed-up in accordance with clinical practice.

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct

- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

All serious adverse events, pregnancy exposures and/or pregnancies in partners for Janssen medicinal products under study should be reported directly by the Sponsor Investigator, **within 24 hours of becoming aware,** to Janssen Scientific Affairs using the Janssen Scientific Affairs Serious Adverse Event Report Form. In the event the study is blinded, the Sponsor Investigator will submit an unblinded SAE or pregnancy exposure report to Janssen Scientific Affairs.

All follow-up information for serious adverse events that are not resolved at the end of the study or by the time of patient withdrawal must be reported directly by the Sponsor Investigator, **within 24 hours becoming aware**, to Janssen Scientific Affairs using the Janssen Scientific Affair's Serious Adverse Event Report Form.

VIII. Product Quality Complaints for Janssen Medicinal Products

A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, investigators, and Janssen Scientific Affairs, and are mandated by regulatory agencies worldwide. Janssen Scientific Affairs has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information. Lot and/or Batch #s shall be collected or any reports of failure of expected pharmacological action (i.e., lack of effect).

All initial PQCs involving a Janssen product under study must be reported to Janssen Scientific Affairs by the Sponsor Investigator **within 24 hours after being made aware of the event.**

If the defect for a Janssen product under study is combined with either a serious adverse event or non-serious adverse event, the Sponsor Investigator must report the PQC to Janssen Scientific Affairs according to the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by Janssen Scientific Affairs.

IX. Maintenance of Safety Information

All safety data should be maintained in a clinical database in a retrievable format. The Institution and Sponsor Investigator shall provide all adverse events, both serious and non-serious, in report format. However, in certain circumstances more frequent provision of safety data may be necessary, e.g. to fulfill a regulatory request, and as such the data shall be made available within a reasonable timeframe at Janssen Scientific Affair's request.

X. Transmission Methods:

The following methods are acceptable for transmission of safety information to Janssen Scientific Affairs:

- Electronically via Janssen SECURE Email service (preferred)
- For business continuity purposes, if SECURE Email is non-functional:

- Facsimile (fax), receipt of which is evidenced in a successful fax transmission report
- Telephone (if fax is non-functional).

Please use the contact information and process information provided by Janssen Scientific Affairs.

XI. Procedures for Reporting Adverse Events (AE), Serious Adverse Events (SAE), Pregnancy, and Product Quality Complaints (PQC) to Janssen Scientific Affairs

a. AEs, SAEs, Special Situations and Pregnancy Reporting.
The Institution and the Sponsor Investigator will transmit SAEs and Special Situations in a form provided by Janssen Scientific Affairs in accordance with Section VIII Transmission methods, in English **within 24-hours** of becoming aware of the event(s).

All available clinical information relevant to the evaluation of a related SAE or Special Situation is required.

- The Institution and/or Sponsor Investigator are responsible for ensuring that these cases are complete and if not are promptly followed-up. A safety report is not considered complete until all clinical details needed to interpret the case are received. Reporting of follow-up information should follow the same timeline as initial reports.

- Copies of any and all relevant correspondences with regulatory authorities and ethics committees regarding any and all serious adverse events, irrespective of association with the Janssen Product under study, are to be provided to Janssen Scientific Affairs using a transmission method in Section VIII **within 24 hours of such report or correspondence being sent to applicable health authorities.**

b. PQC Reporting
The Institution and the Sponsor Investigator will report any suspected PQC to the Janssen contact within 24 hours of becoming aware of the complaint. The product should be quarantined immediately and if possible, take a picture.

XII. Reconciliation of SAEs

At a minimum, on a quarterly basis and at the end of the Study, Janssen Scientific Affairs will provide to the Institution and/or Sponsor Investigator, a listing of all SAEs reported to Janssen Scientific Affairs. The Sponsor Investigator will review this listing and provide any discrepancies to Janssen Scientific Affairs.

Upon request, Institution and/or Sponsor Investigator shall provide Janssen Scientific Affairs with a summary list of all SAEs, and AEs of Special Interest and Special Reporting Situation reports to date, for reconciliation purposes.

XIII. Dissemination of Safety Information from Janssen Scientific Affairs to Institution/Sponsor Investigator Sponsor Investigator will be responsible for submitting IND safety reports for the Study Product to Institution's IRB in accordance with Federal regulations 21 CFR 312.66.

Janssen Scientific Affairs agrees to provide to the Sponsor Investigator IND safety reports for the Study Product as they become available until all subjects in the Protocol have completed their last Study visit according to the Protocol (i.e. Last Subject Last Visit has occurred).

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