CLINICAL RESEARCH PROJECT **Protocol # 13-H-0123**
IND: Exempt

NHLBI Protocol:

An Exploratory Study to Evaluate the Effects of Roflumilast on Insulin Sensitivity and Metabolic Parameters in Pre-diabetic Overweight and Obese Individuals

Short Title: Roflumilast and Insulin Action

Keywords:*Roflumilast,Phosphodiesterase-4; Pre-diabetes; Incretins; Insulin Action; and Insulin Secretion*

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Subjects in study at NIH:	Number	Gender	Age range
	50	M, F	30-65

Multi-center trial:	No
Ionizing Radiation for Research:	Yes
Off-Site Project:	No
DSMB Involvement:	No
Tech Transfer:	No
IND/IDE:	No (FDA IND Exemption 04/19/2012)

IND Sponsor: Not Applicable

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1. Précis

Resveratrol, a polyphenol most notably found in red wine has anti-aging properties in mice fed a high-fat diet; resveratrol protects against obesity and type 2 diabetes. Several clinical trials have been conducted to study the metabolic effects of resveratrol. Although these trials have used different subject groups (e.g. obese healthy, type 2 diabetics or older adults with glucose intolerance), they suggest that resveratrol may improve insulin sensitivity. However, the therapeutic potential of resveratrol is diminished by the fact that it has a very promiscuous target profile. In order to translate resveratrol biology into clinical application, it is helpful to identify the cellular target(s) of resveratrol that mediate the desired effects and to develop therapies specific for that target(s). Recently, we discovered that the metabolic effects of resveratrol appear to result from competitive inhibition of cAMP-degrading phosphodiesterases (PDEs), which increases cAMP levels. The cAMP-dependent pathways activate AMP-activated protein kinase (AMPK), which is essential for the metabolic effects of resveratrol. Inhibiting PDE4 with rolipram reproduces all of the metabolic benefits of resveratrol, including protection against diet-induced obesity and an increase in mitochondrial content, fat oxidation, physical stamina and glucose tolerance in mice. Based on results from cellular and preclinical studies, we hypothesize that PDE4 inhibition will ameliorate insulin resistance in pre-diabetic individuals. To test these hypotheses, we will conduct an exploratory study on the potential beneficial effects of roflumilast (Daxas®), a PDE4 inhibitor, on insulin sensitivity in pre-diabetic individuals. Each study participant will receive oral roflumilast (250 μg, once a day for 2 weeks, followed by 500μg once a day for 4 weeks). At baseline and after the 6-week treatment period, we will assess insulin sensitivity (hyperinsulinemiceuglycemic glucose clamp technique, “glucose clamp”).In addition, β-cell function, skeletal muscle mitochondrial function, body composition, and circulating adipocytokine profile will be measured at baseline and after treatment to evaluate potential changes that may be related to improvements in metabolic function. Vascular function is not only an indicator of insulin sensitivity, but is also important for glucose delivery and metabolism. If possible, vascular function will be assessed along with the other parameters at baseline and after treatment with roflumilast. Regarding vascular function, we may measure basal and insulin-stimulated brachial artery blood flow (large conduit artery assessed by Doppler ultrasound) as well as capillary recruitment in forearm skeletal muscle (small nutritive arterioles assessed by ultrasound with microbubble contrast). This study will explore whether roflumilast is effective at improving insulin sensitivity in pre-diabetic individuals. Results from this study may have important implications for the potential use of roflumilast in treating type 2 diabetes.

2. Introduction

In the United States, obesity and its related complications such as diabetes and cardiovascular disease has risen to near epidemic proportions resulting in significant morbidity, mortality, and health care costs. Consequently, there is considerable scientific and public interest in the efficacy of dietary and pharmacological interventions that may ameliorate obesity and the associated cardio-metabolic states. Phosphodiesterases (PDEs) have a key regulatory role in the cAMP pathway, as they are the only known mechanism for inactivating cAMP by its catalysis to 5′-AMP. Genetic ablation or pharmacological inhibition of PDE4 reduces inflammation and prevents diet-induced obesity in rodent models. In fact, the potent anti-inflammatory actions of PDE4 inhibitors underlie the basis for their therapeutic use in exacerbation of chronic obstructive pulmonary disease (COPD). Roflumilast, a selective PDE4 inhibitor, improves lung function and other clinical outcomes in patients with chronic obstructive pulmonary disease (COPD). An unexpected finding from post-hoc analysis of pooled data from previous roflumilast trials was that in patients with COPD and comorbid type 2 diabetes, roflumilast reduced fasting blood glucose and hemoglobin A1c (HbA_{1c}) levels (2). A subsequent double-blind, randomized parallel-group study showed that roflumilast decreased blood glucose and HbA_{1c} levels in patients aged 35-70 years with newly diagnosed type 2 diabetes who were treatment naïve (3). Glucose decreased by 1.04 mmol/L and HbA_{1c} decreased by 0.79%. As seen in prior trials, roflumilast decreased body mass index by -0.26kg/m^2 more than with placebo. However, the mechanisms mediating this hypoglycemic effect are unknown. Presumably, the glucose lowering effect of roflumilast is mediated by cAMP signaling since such a small decrease in body weight would not be expected to decrease glucose significantly. However, the gastrointestinal side-effects associated with roflumilast such as diarrhea and nausea may also contribute to the hypoglycemic effects. Even if cAMP signaling is responsible for the hypoglycemic effects of roflumilast, the mechanisms by which cAMP signaling can decrease plasma glucose levels have not been elucidated. In rodent studies, we have shown that PDE4 inhibition increases basal metabolic rate, augments mitochondrial function, and improves insulin sensitivity (4).The observation that thefasting levels of insulin, adiponectin and leptin were not changed by roflumilast does not argue against this hypothesis because insulin sensitivity is reflected by a combination of insulin and glucose levels (5). Fasting insulin levels usually reflect hepatic insulin sensitivity. Therefore, it is possible to increase insulin sensitivity and decrease glucose without affecting fasting insulin levels if the muscle insulin sensitivity is increased more than hepatic insulin sensitivity. In addition, cAMP signaling has been shown to increase insulin secretion (1), raising the possibility that roflumilast may improve glucose tolerance by improving both insulin sensitivity and secretion. Based on these observations, we hypothesize that oral administration of roflumilast will increase: insulin sensitivity, β-cell function, vascular function, mitochondrial function and favorably alter body composition and circulating adipocytokine profile in prediabetic overweight and obese individuals. This population has been chosen as the individuals will have impaired glucose and insulin, but will not have been treated with diabetic medications.

3. Background

Preliminary data: Resveratrol inhibits PDE4 and increases insulin sensitivity.

Resveratrol is a natural polyphenol produced by plants in response to environmental stress (6) and is present in many plant-based foods, most notably red wine. In mice, long-term administration of resveratrol induced gene expression patterns that resembled those induced by calorie-restriction and delayed aging-related deterioration (7). Resveratrol also protected against obesity and increased insulin sensitivity in rodents fed a high calorie diet (8,9) and in type 2 diabetic patients (10), suggesting that the pathway targeted by resveratrol might be important for developing therapies for type 2 diabetes.
Mitochondrial function, particularly in skeletal muscle, is crucial for insulin sensitivity because decreased mitochondrial oxidation of fat leads to accumulation of intramyocellular lipids, which leads

to insulin resistance. Individuals with type 2 diabetes have reduced skeletal mitochondrial content and function. The anti-diabetes property of resveratrol is mediated by activating 5'-AMP-activated kinase (AMPK), particularly in skeletal muscle (8,11-14). AMPK is a heterotrimeric protein consisting of a catalytic subunit and two regulatory subunits, β and γ. Activation of AMPK has been shown to reduce fat accumulation and increase glucose tolerance, insulin sensitivity, and mitochondrial function in skeletal muscle and physical endurance (15-18). It is believed that AMPK is also a target of metformin, a first line type 2 diabetes drug. A hint that cAMP may mediate the metabolic effects of resveratrol, including activation of AMPK, was suggested by a previous study reporting that resveratrol increased cAMP production in breast cancer cells (19). Therefore, we investigated whether resveratrol increased cAMP levels in myotubes. As shown in Figure 1A, cAMP levels increased significantly with resveratrol. Similarly,cAMP levels were elevated inskeletal muscle and white adipose tissue in resveratrol treated mice. The possibility that the increase in cAMP production was responsible for the activation of AMPK by resveratrol was examined by treating myotubes with resveratrol in the presence of the adenylyl cyclase (AC) inhibitor MDL-12,330A (Figure 1B). MDL-12,330A prevented resveratrol (50 μM) from increasing the phosphorylation of both AMPK (T172) and the AMPK substrate acetyl-CoA carboxylase (ACC) (S79), which are markers of AMPK activity. These findings indicate that cAMP signaling is essential for resveratrol to activate AMPK.

The intracellular levels of cAMP are determined by the activities of AC, which synthesize cAMP from ATP and cyclic nucleotide phosphodiesterases (PDEs), which hydrolyze cAMP or cGMP to AMP or GMP, respectively. We measured the effect of resveratrol on the activity of AC types 2, 6, and 8, which represent the three major subclasses of the ten ACs in mammals. We found that resveratrol had no effect on AC activity, either in the basal state or in the activated state (+forskolin), suggesting that resveratrol increased cAMP levels by inhibiting PDEs.

The PDE superfamily is comprised of 11 families (PDE1-11) and each family contains a number of different isoforms. We measured the activities of recombinant PDE1, 2, 3, 4 and 5 in the presence of resveratrol. We found that resveratrol did not inhibit PDE2 or PDE5 but competitively inhibited PDE1 (IC_{50}~6 μM), PDE3 (IC_{50}~10 μM) and PDE4 (IC_{50}~14 μM) (Figure 2). PDE4 is the predominant PDE in skeletal muscle. If the metabolic effects of resveratrol result from inhibiting PDE4 in skeletal muscle, a known PDE inhibitor should produce metabolic effects very similar to those produced by resveratrol. To test this hypothesis, we treated mice on high-fat diet with PDE4 inhibitor rolipram (2 mg/kg/d). After 12-14 weeks of treatment, we isolated skeletal muscle and measured the mRNA levels of genes that are known to be induced by resveratrol and AMPK such as eNOS, PGC-1α and others important for mitochondrial biogenesis. We found that rolipram consistently increased the mRNA levels of these genes. In agreement with this, treatment with resveratrol, rolipram and cAMP induced mitochondrial biogenesis in C2C12 myotubes to comparable levels. Rolipram and resveratrol also increased mitochondrial content to similar levels in mouse skeletal muscle (Figure 3A). To determine whether increased mitochondrial function improved exercise tolerance, we exercised rolipram-treated mice on a treadmill. Rolipram-treated mice ran a significantly greater distance on a treadmill before exhaustion than control mice (445±19 m vs. 268±50 m) (Figure 3B). Taken together, these findings indicate that in regard to mitochondrial function in skeletal muscle, rolipram and resveratrol have very similar metabolic effects. The similarity between the effects of rolipram and resveratrol also extended to the white adipose tissue (WAT). As was the case with resveratrol-treated mice (13,20), the phosphorylation levels of AMPK and ACC were increased in the WAT of rolipram-treated mice. C57BL6/J mice treated with rolipram were resistant to weight gain on a high fat diet and had less fat content even though their food intake was similar to that of control mice. Decreased weight gain despite normal food intake suggests that rolipram increased the metabolic rate. Indeed, oxygen consumption rate was increased inrolipram-treated mice (Figure 3C), but physical activity levels were not affected indicating that rolipram increased the basal metabolic rate. Rolipram-treated mice were more glucose tolerant (Figure 4A) and insulin sensitive (Figure 4B) than were control mice Taken together, these

findings indicate that PDE4 inhibition reproduces all the metabolic benefits of resveratrol such as increased mitochondrial function in skeletal muscle, metabolic rate and insulin sensitivity. Therefore, PDE4 inhibitors such as roflumilast may also decrease body weight and lower glucose by increasing mitochondrial function and increasing insulin sensitivity.

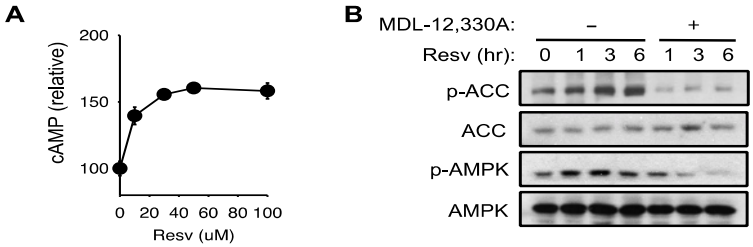

*Figure 1.**A.**cAMP levels in myotubes 30 min after treatment with resveratrol. **B.** Phosphorylation of ACC, an AMPK substrate, and AMPK in myotubes treated with resveratrol in the presence of adenylyl cyclase inhibitor MDL-12,330A*

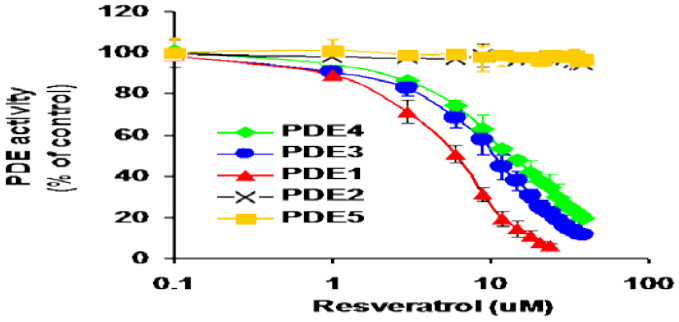

Figure2. Inhibition curve of PDEs with resveratrol.

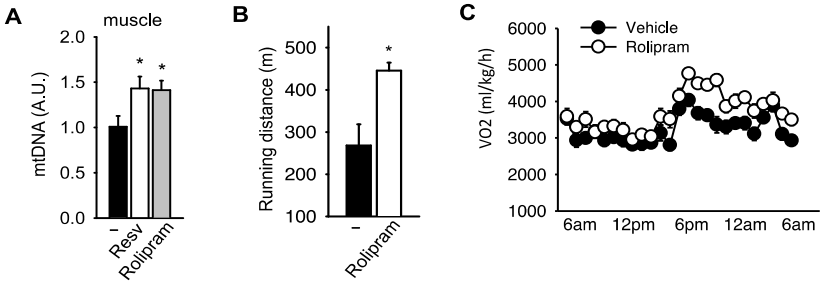

*Figure 3. In mice, PDE4 inhibitor rolipram increases **A.** mitochondrial density in skeletal muscle as measured by mitochondrial DNA (mtDNA) content, **B.** Maximal running distance on treadmill, **C.** Metabolic rate.*

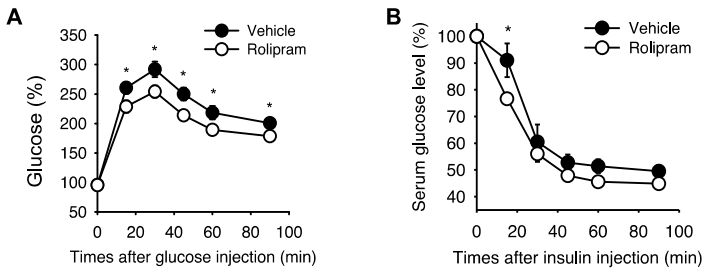

*Figure 4. Rolipram improves **A.** glucose tolerance and **B.** insulin sensitivity in mice.*

3.1 Hypothesis

Oral administration of a phosphodiesterase-4 inhibitor, roflumilast for 6 weeks improves insulin sensitivity in pre-diabetic overweight/obese individuals.

4. Objectives and Specific Aims

4.1 Primary Objective

Determine if oral administration of roflumilast (250 mcg p.o. once a day for 2 weeks followed by 500 mcg p.o. once a day for 4 weeks) improves insulin sensitivity as assessed by the hyperinsulinemic euglycemic glucose clamp technique in prediabetic overweight/obese subjects.

4.2 Secondary Objective

4.2.1 Determine if oral administration of roflumilast (250 mcg p.o. once a day for 2 weeks followed by 500 mcg p.o. once a day for 4 weeks) improves β-cell function in pre-diabetic overweight/obese subjects as assessed by the mixed meal test.

4.2.2 Determine if oral administration of roflumilast (250 mcg p.o. once a day for 2 weeks followed by 500 mcg p.o. once a day for 4 weeks) augments postprandial plasma incretin concentrations as assessed by the mixed meal test.

4.2.3 Determine the effects of oral roflumilast on circulating levels of adipokines, cytokines, and inflammatory markers (adiponectin, leptin, hs-CRP, TNF-α, plasma intracellular adhesion molecules (ICAM-1) and vascular cell adhesion molecule (VCAM-1)).

4.2.4 Determine if oral roflumilast alters: total body fat and lean body mass measured by dual-energy x-ray absorptiometry (DEXA); total abdominal fat mass and its distribution in subcutaneous and intra-abdominal compartments measured by MRI/MRS.

4.2.5 Determine, if possible, if oral roflumilast improves vascular function in prediabetic overweight/obese subjects as assessed by vascular ultrasound and contrast-enhanced ultrasound (CEU) techniques.

5. Investigational Plan

5.1 Study Design and Methods

The exploratory study will utilize an open label, non-randomized, single arm pre-post study design to test our hypotheses. Subjects will receive oral roflumilast (250 mcg p.o. once a day for 2 weeks followed by 500 mcg p.o. once a day for 4 weeks) tablets for 6 weeks. The two-step dose is aimed

at maximizing tolerability to roflumilast. Fasting hepatic glucose production (by ^{2}H-6-glucose infusion), glucose clamp, DEXA scan, abdominal MRI/MRS scan, and muscle and adipose tissue biopsies (optional) will be performed on all subjects at the beginning of the study and after the 6-week treatment course. Muscle and adipose tissue biopsies are optional. The tests for vascular function will be optional as well and will depend on whether or not the cardiology research team is available to do the vascular studies at the time of the clamp studies, the latter which is essential to our primary outcome. These studies will all be performed in the facilities of the NIH Clinical Research Center.

5.2 Description of Study Population and Eligibility

Fifteen men and women between the ages of 30 and 65 in good general health, except for body mass index (BMI) >24.9 and <39.5 kg/m^2 with pre-diabetes and currently not on any pharmacological regimens or nutritional supplements that affect insulin sensitivity will be recruited. The goal will be for 12 subjects to complete all study procedures, thus a sample size of 15 will allow for dropouts and withdraws. However, we are requesting to consent and screen on this protocol up to 50 participants to obtain the 15 eligible for treatment. Thus, up to 50 participants may be enrolled into this protocol.

5.2.1 Eligibility Criteria

5.2.1.1 Inclusion Criteria

- Adult, weight- and diet-stable men and women in good general health with no significant underlying illnesses and normal or clinically insignificant results (medical histories, laboratory profiles, physical examination, and electrocardiograms),
- Women must be non-pregnant or post-menopausal, or women of childbearing potential must be non-lactating and using an effective form of birth control during and for 30 days after the study period (partner's use of condoms or partner's vasectomy is not an acceptable contraception method for this study) ,
- Must be 30 - 65 years of age, inclusive
- Body Mass Index (BMI) > 24.9 and <39.5 kg/m^{2}with a stable (± 2.5 kg) weight for the last 6 months by history,
- Pre-diabetes, as defined by a fasting blood glucose of greater than 100 mg/dL and less than 126 mg/dL and/or A1C equal to or greater than 5.7 and less than or equal to 6.5 %
- Subjects must be able to understand the protocol and provide written informed consent.

5.2.1.2 Exclusion Criteria

- Women will be excluded from our study if they are pregnant, breastfeeding, or if they plan to become pregnant prior to the end of the study,
- Cannot be on any medications including multivitamins or nutritional supplements that in the investigator’s opinion will affect insulin sensitivity
- Currently taking systemic corticosteroids, insulin, or anticoagulants, anxiolytics, ketoconazole, erythromycin, cimetidine, enoxacin, strong CYP 3A4/1A2 inducers (e.g., rifampicin, phenobarbital, carbamazepine, phenytoin), birth control pills containing gestodene and ethinyl estradiol, use food supplements that cannot be discontinued, or any other medication that the investigators deem a contraindication.

- AST or ALT >3 times the upper normal limit
- Hepatitis B antigen, HIV or C positive antibody tests,
- Liver disease, pulmonary disease, renal insufficiency (serum creatinine > 1.5mg/dl), coronary heart disease, heart failure (New York Heart Association heart failure Class III or IV), peripheral vascular disease, coagulopathy.
- History of or current diagnosis of major depressive disorder, or history of or current diagnosis of other psychiatric disorders that in the opinion of the investigator would make participant unsafe for the participant.
- Currently being treated for any form of cancer or have a history of cancer, that in the investigator's judgment would not make the participant a candidate for the study for safety or scientific reasons.
- Claustrophobic,
- On a weight loss program with ongoing weight loss, or a history of eating disorders. Actively using tobacco products or have used tobacco products within last year (>3 cigarettes/day), regular alcoholic beverage intake of more than two drinks per day. Subjects with any condition that would have made them, in the opinion of the principal investigator (PI), unsuitable for the study.
- Subjects with a contraindication for the ultrasound contrast agent.

5.3 Study Procedures

5.3.1 Recruitment

Subjects will be recruited through advertisements in cooperation with the NIH Clinical Center Patient Recruitment and Referral Center and/or the Clinical Research Volunteer Program.

Advertisements may be placed in local newspapers or other mediums in order to reach a wide variety of ethnic and racial groups. Flyers may also be placed on campus as well as the surrounding metropolitan area.

Subjects may also find information about trials through the NIH, Clinicaltrials.gov, and NHLBI Internet recruitment sites.

The contact information provided in all advertisements will be the NIH Clinical Center Patient Recruitment and Referral Center.

When potential participants contact the NIH Clinical Center Patient Recruitment and Referral Center about the study, they are asked questions concerning basic eligibility for the study. Participants that appear to be suitable candidates will be referred to the study team.

The study team will contact the potential participant. The study team will schedule a screening appointment at the NIH CC to obtain informed consent and perform the eligibility assessment. If the participant requests a copy of the consent prior to the screening appointment, the consent may be faxed, emailed, or mailed to the potential participant.

Based on recruitment data from prior studies, we propose to screen 50 participants to obtain the 12 eligible for treatment. Thus, we propose to have a recruitment ceiling of 50.

5.3.2 Informed Consent

Informed consent will be obtained prior to eligibility assessment procedures being performed. Up to 50 participants will be consented under this protocol and screened in order to ensure that 15 participants receive treatment. Thus, up to 50 may be enrolled into this protocol. See section 10.6 for detailed information on the process.

5.3.3 Eligibility Assessment

Screening procedures will be performed prior to the start of treatment. Screening procedures for enrollment will include the following:

- **Medical History and Physical Examination**
  - A thorough medical history (including queries regarding psychosocial history, diet, physical activity and the use of nutritional supplements or complementary and alternative medicine therapies, prior history of patent foramen ovale (the latter which would be a contraindication to the ultrasound contrast agent)), and a physical examination.
- **BMI assessment**
- **Baseline electrocardiogram**
- **Clinical Laboratory tests**
  - CBC w/differential
  - Electrolytes (Sodium (Na), Potassium (K), Chloride (Cl), Bicarb (HCO_3))
  - liver function tests (Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Direct Bilirubin),
  - Creatinine and BUN
  - urinalysis,
  - plasma glucose,
  - plasma insulin,
  - lipid profile (Total Cholesterol, Triglycerides, HDL Cholesterol, LDL Cholesterol (calculated)),
  - C-peptide,
  - HbA_{1C},
  - free fatty acids (FFA),
  - highly sensitive C-reactive protein,
  - thyroid stimulating hormone function tests
  - HIV, and hepatitis B and C antibody tests
  - Serum pregnancy test
- **Psychiatric Evaluation of Suicidal Ideation, Major Depression, Quality of Life, and other disorders**
  - **Structured Clinical Interview for DSM Disorders (SCID)**

    The SCID will be administered by a trained AI from NIMH. The presence or absence of past and current episodes of major depression will be evaluated by administering a structured psychiatric interview called SCID-IV.{American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders: DSM-IV 1994} Completion of the psychiatric interview usually takes 40 minutes, but can take as long as two hours. If a psychiatric disorder is found during the evaluation, the patient will be referred to the NIH consultation service or, if he/she prefers, they will be referred to a provider in the community.

  - **Columbia Suicide Severity Rating Scale (C-SSRS)**

    The Columbia Suicide Severity Rating Scale (C-SSRS) will be employed to

evaluate suicidal ideation. A baseline assessment will be performed prior to administration of investigational product at screening. Then the subjects will be evaluated at each visit to the clinical center (21-22). This scale is being administered due to roflumilast's black box warning of suicidal ideation.

The C-SSRS is a validated measure on suicidal ideation (21-22) and is recommended by the FDA for use in clinical trials using drugs that have been shown to potentially cause suicidal ideation (22).

If the result of the C-SSRS, at any point in this study, indicates the participant is having thoughts of suicide and has the potential to act of those thoughts, the participant will be removed from the study and be referred for a psychiatry consult. Additionally, the participant will be followed to make sure the appropriate inventions are provided to resolve the event.

- **Quality of Life Enjoyment and Satisfaction Questionnaire (Q-Les-Q)**
  The Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) is a self-report measure designed to measure the degree of enjoyment and satisfaction experienced by participants (25).

Best efforts will be made to admit research subjects within three months after the initial screening visit. If more than three months have elapsed between the initial clinic screening visit and the planned inpatient admission date, research subject will be asked to repeat screening laboratory tests prior to the proposed inpatient admission. These laboratory tests will be repeated to ensure that there is no interval change in the test results and will be performed within two days prior to the proposed admission date. Clinically significant deviations from the initial screening results will lead to exclusion of the subject from the inpatient admission at that time. Decision on whether or not to re-consider the subject for continued participation in the study in the near future will be according to the clinical judgement of the research team. The research team may choose to evaluate the subject in clinic within two days prior to the planned admission to facilitate decision making about whether or not to proceed with the admission.

Participants who do not undergo their first inpatient admission within six months after the initial screening visit will be removed from the study.

- **Diet and Exercise Assessment:**

  For one day before admission (day -1 or -2 before admission) and the 3 days during admission to the NIH Metabolic Clinical Research Unit (MCRU) for visits 1 and 4, each subject will be provided with a weight-maintenance diet using a standard diet composition of 55% of energy from carbohydrate (minimum of 150 grams of carbohydrate), 30% of energy from fat, and 15% of energy from protein on an out-patient basis. The food will be supplied by the Clinical Center Metabolic Kitchen and subjects may eat one meal per day on the MCRU if their outpatient visit occurred the day prior to admission. The rest of the meals and snacks will be packed out for them to take home. If the subject's outpatient visit occurred 2 days prior to admission, then the meals for the next day (that is 1 day prior to admission) would be packed for them to take home. The daily caloric content of the diet during the out-patient segment will be determined by the Mifflin-St Jeor equation based on age, gender, height, weight, and an activity factor of 1.4.

  During screening, a dietitian will provide detailed instruction regarding the accurate

completion of 3-day food records (2 weekdays and 1 weekend day) to each subject. Subjects will be instructed to record their intake for the same three days that they wear the accelerometers just the week prior to each visit. Dietetic professionals will review all food records using three-dimensional food models with participants at visits 1 and 4 before coding the food records into Nutrition Data System for Research (NDSR, Minneapolis, MN).

5.3.4 Baseline – Visit 1

Baseline procedures will be conducted over four days, to be designated as (Day -2 or Day -1), Day 1, Day 2 and Day 3. The first day (Day -2 or Day -1), participants will report to the MCRU as outpatients. The reason for having participants report on either 1 or 2 days prior to admission is to provide flexibility in scheduling for the participants and the research coordinator. For the second part of visit 1 (Day 1), participants will be admitted to the NIH CC MCRU as inpatients for 3 days and 2 overnights. The following procedures will be performed during this time period:

- **Diet and Exercise Assessment (Day -2/-1):**

  For one day before admission to the NIH for inpatient visits 1 and 4, and for the three days during each inpatient admission, each subject will be provided with a weight-maintenance diet using a standard diet composition of 55% of energy from carbohydrate (minimum of 150 grams of carbohydrate), 30% of energy from fat, and 15% of energy from protein on an out-patient basis. The food will be supplied by the Clinical Center Metabolic Kitchen and subjects may eat one meal per day on the MCRU; the rest of the meals and snacks will be packed out for them to take home. The daily caloric content of the diet during the out-patient segment will be determined by the Mifflin-St Jeor equation based on age, gender, height, weight, and an activity factor of 1.4.Weight and BMI will be measured as part of this assessment.

- ***Assessment of hepatic and peripheral insulin sensitivity (Day +2):***

  The hepatic insulin-resistance index is the product of hepatic glucose production (HGP) and the corresponding plasma insulin concentration. In order to measure the differences in HGP we plan to assess fasting glucose kinetics with stable isotope technique. Basal endogenous glucose production will be determined using deuterium glucose as tracer. [6,6$^2H_2$] glucose will be administered intravenously initially as a bolus (5.1 mg/kg) then at the rate of 0.072 mg/kg/min. After a three-hour infusion, blood samples will be collected at times 0, 10', 20', and 30' minutes (+/- 5 minutes for all time points), and [6,6$^2H_2$] -glucose levels will be determined by mass spectrometry. HGP will be assessed pre- and post-treatment intervention after an overnight fast.

  Hyperinsulinemic Euglycemic Glucose Clamp (Day +2) - This is the gold-standard test to determine insulin sensitivity. Urinary pregnancy test will be done to exclude pregnancy where applicable. Using a four way parallel port, lines for infusing glucose (D20W), insulin, potassium phosphate (0.09 mEq/ml) and normal saline will be connected to a 20 gauge intravenous cannula placed in one arm. Alaris pumps will be used to control the rates of infusion for glucose, potassium phosphate, and saline. Insulin will be infused at a constant rate (40 mU/m²/min), following a loading dose at double the rate for the first 8 min. To assess suppression of hepatic glucose production during clamp, [6,62H2]-glucose will be infused at a rate of 0.0182 mg/kg/min for approximately 3 hr. Potassium phosphate will be infused up to a maximum rate of 10 mmol/hr (15 mEq K^+/hr) to prevent hypokalemia. The glucose infusion rate will be adjusted to maintain blood glucose at the fasting level for each patient. The rate of

potassium phosphate infusion will be adjusted throughout the clamp period, according to empiric judgment of the patient's insulin sensitivity (as demonstrated by the ongoing changes in glucose infusion rate), not to exceed the maximum rate specified above. A second peripheral intravenous catheter will be placed in the opposite arm and will be used for obtaining blood samples for glucose determination. The arm used for sampling will be warmed with a heating blanket in order to arterialize the blood. 0.5 ml blood samples for measuring blood glucose will be obtained on the following schedule: 10 and 5 minutes prior to beginning the insulin infusion; every 5 - 10 minutes until completion of the study (approximately 3 additional hours). Blood samples will be analyzed immediately for determination of blood glucose concentration using a YSI 2700 dual chamber blood glucose analyzer. In addition, 1 ml blood samples will be taken for insulin determination 10 and 5 minutes before insulin infusion, at initiation of insulin infusion, and at 20 - 30 minute intervals after the beginning of insulin administration. 1 ml blood samples for potassium levels are also taken before initiation of clamp infusions and 1 hour after insulin infusion has been stopped. After the clamp portion of the study, the insulin infusion will be turned off and the patient will be weaned from the glucose infusion over the next 2 hours while also eating a high carbohydrate, high protein meal.

- ***Measurement of plasma incretins, circulating inflammatory markers and adipocytokines:***

  Plasma incretin, adiponectin, leptin, adhesion molecules, TNF-α, and MCP-1 levels will be measured by Millipore, Billerica, MA.

- ***Measurements of brachial artery flow and forearm capillary recruitment (Day +2):*** When administratively possible to schedule, brachial artery flow and forearm capillary recruitment will be assessed at baseline and during the steady-state period of the glucose clamp (2 h after initiation of insulin infusion) as previously described (Am J ClinNutr. 2008 Dec;88(6):1685-96). For measurement of brachial artery flow, Doppler ultrasound will be used. An ultrasound system with a linear array transducer with a transmit frequency of 7.5 MHz will be used for 2-D imaging in long-axis. Brachial artery diameter will be measured using on-line video calipers. Measurements of capillary recruitment will be assessed by using the contrast-enhanced ultrasound (CEU) technique during continuous microbubble infusion. Definity microbubbles that are FDA approved (octafluoropropane gas encapsulated in an outer lipid shell; Bristol Myers Squibb, N. Billerica, MA) will be used for all of the studies. One vial of microbubbles (1.3 ml) will be used for baseline measurement of capillary recruitment while a second vial will be used to assess capillary recruitment at 2 hours after initiation of the insulin infusion for the glucose clamp. Microbubbles will be intravenously infused using a Medfusion syringe pump at a rate of 150 ml/hr for approximately 10 min. Deep flexor muscles of the right forearm will be imaged in two dimensions at a transaxial plane 5 cm distal to the antecubital fossa. Power imaging will be performed. Once Definity microbubbles reach a steady-state concentration (2 min after initiation of microbubble infusion), imaging at pulsing intervals of 0.2 to 15 seconds will be conducted. This allows for progressively greater replenishment of microbubbles in the ultrasound beam. The digitally acquired images will be transferred to an offline computer for further analysis. Data analysis will include estimation of the rate of increase in capillary density and the absolute capillary density both at baseline and at two hours after initiation of the insulin infusion.

- ***Radiologic Assessments (Day -2/-1 or on Day +1, +3):***

- ***Dual energy x-ray absorptiometry (DEXA)*** - With this technique, one can determine total and regional body fat and fat-free masses and can estimate appendicular muscle mass.
- ***Assessment of visceral, liver, and skeletal muscle fat content and distribution*** - Magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) are used to quantify triglyceride content in the abdominal cavity, liver and muscle. Multi-echo imaging using the 3.0 T magnet will be employed to measure ectopic fat.

- ***Optional Skeletal Muscle Biopsy (Day -2/-1 or Day +1):***

  To directly evaluate mitochondrial respiratory function (respiration and respiratory coupling and mitochondrial biogenesis genomic and proteomic analysis) skeletal muscle biopsies will be performed by general surgeons at the NIH Clinical Center, before and after roflumilast. The muscle biopsy is a routine outpatient procedure that is performed using local anesthesia. Under sterile conditions, an excisional biopsy of 400 mg of muscle will be obtained from the subject's calf or thigh. Each subject will undergo a total of two muscle biopsies: one at baseline and one after therapy with roflumilast.

  The muscle biopsy specimen will be divided into three parts. The first part will be snap frozen in liquid nitrogen for subsequent genomic, proteomic and enzymatic analysis. The other half will be transported to the laboratory in an ice-cold buffer (KE) containing 0.18M KCl and 0.01 M EDTA (pH 7.4) immediately following the biopsy. This latter sample will be used for mitochondrial biochemical analysis.

  To evaluate whether the genomic control of mitochondrial respiration is altered in response to roflumilast, mitochondrial DNA copy number and the expression of genes known to regulate mitochondrial biogenesis and function.

  A sample of the skeletal muscle will be stored at -80 degrees C for subsequent proteomic assessment.

  All identifying data in stored specimens including name, social security number, medical record number or date of birth will be removed. Only the study subject ID will be kept at the NHLBI will link the specimen to the subjects in the study.

- ***Optional Adipose tissue biopsy (Day -2/-1 or Day +1):***

  To measure mRNA levels of "beige fat" markers, including Prdm16, Cox8b and UCP1 by using real-time PCR (23), adipose tissue biopsies will be performed by general surgeons at the NIH Clinical Center, before and after roflumilast. Subcutaneous adipose tissue (3-5 g) will be removed from the abdominal region or thigh by aspiration with a 16-gauge needle under local anesthesia (2% xylocaine). Connective tissue will be removed. A representative portion of the tissues will be formalin fixed, paraffin embedded, sectioned, and stained using standard histological methods. Slides will be examined visually to assess cell populations/tissue composition to insure that morphologically similar tissue biopsies were sampled over time. The remaining tissue will be separated into aliquots of approximately 500 mg from adipose tissue specimens for RNA isolation and protein extraction, flash frozen in liquid nitrogen and stored at -80ºC for future studies.

- ***PBMC collection:***

  Before the beginning of each clamp study, the subjects will have 10 mL blood drawn

to collect PMBCs to look at the mitochondrial biogenesis gene profile.

- ***Blood Samples for Future Biochemical Studies:***

  Before the beginning of each clamp study, the subjects will have between 10 - 20 mL blood drawn to be stored so that determination of plasma analytes that are not currently anticipated may be made in the future.

- **Clinical Labs:**
  - Electrolytes (Na, K, Cl, HCO_3)
  - Liver Function Tests (Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Direct Bilirubin)
  - CBC w/differential
  - Serum creatinine
  - BUN
  - urinalysis,
  - plasma glucose,
  - plasma insulin,
  - lipid profile: (Total Cholesterol, Triglycerides, HDL Cholesterol, LDL Cholesterol (calculated)),
  - lipoprotein profile: Plasma lipid analysis, including VLDL, LDL and HDL particle size and number are measured by nuclear magnetic resonance (NMR) spectroscopy using the Vantera Clinical Analyzer (LipoScience Inc., Raleigh, North Carolina) in the Clinical Center. This clinical test which quantifies VLDL-P, LDL-P and HDL-P based on lipoprotein particle size using the amplitudes of their distinct lipid methyl group NMR signals to calculate the different lipoproteins. Lipoprotein particles is further subdivided into large, medium, and small particles based on the mean particle sizes as the weighted average of related subclasses. The rationale for adding this test is that cyclic AMP (cAMP) signaling in the liver decreases lipid synthesis. Therefore, it is possible that roflumilast, by increasing cAMP and activating protein kinase A, may decrease hepatic lipid production.
  - C-peptide,
  - free fatty acids (FFA), Hemoglobin A1C
  - highly sensitive C-reactive protein,
  - Serum pregnancy test

The following procedures will be performed on the third day of the inpatient visit.

- ***Mixed Meal Stimulation Test (Day +3)*:**

  On the third day of hospitalization, the effect of a standardized liquid meal of standard macronutrient contents on glucose, insulin, and gut peptides will be assessed following an overnight fast. During the mixed meal stimulation test, we will administer a liquid meal of known macronutrient composition. Blood samples will be obtained at baseline, 15, 30, 45, 60, 120 and 180, 240 and 300 minutes (+/- 5 minutes for all time points) after consuming the liquid meal.

- ***Drug Dispensing and first dose (Day +3, first inpatient visit)***

  The pharmacy will dispense 2 weeks and 2 days of tablets containing 250 mcg of roflumilast (half of commercially available 500 mcg tablet). The subject will be instructed to take the first dose from the supply provided by the pharmacy while still in the clinical center and will be observed for approximately two hours after the taking

the first dose.

- ***Study Drug Diary:***

  Each participant will be provided a study drug diary and instructed to record on a in the diary each time they take the study drug. The study drug diary will be reviewed at each visit to ensure compliance.

5.3.5 Week 2, Visit 2 Procedures: (+/- 2 days)

The following procedures will be performed at this visit.

- AE Assessment
- Pill count and review of study drug diary
- Dose Escalation
  - Subjects' dose will be increased to 500 mcg p.o. Subjects will be instructed to take one 500 mcg tablet a day.
- Dispensing of enough drug to last the participant 4 weeks plus 4 days

5.3.6 Week 3, Visit 3- Procedures (+/- 4 days)

The following procedures will be performed at this visit.

- AE Assessment
- ECG
- Clinical Labs:
  - Electrolytes (Na, K, Cl, HCO3)
  - Liver Function Tests (Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Direct Bilirubin)
  - Serum creatinine, BUN
  - Pregnancy test
- Pill count and review of study drug diary

5.3.7 Week 5 - Accelerometer and Food Record

Participants will complete the 3-day food records (2 week days and 1 weekend day) and wear the accelerometer on the same 3 days one week prior to Visit 4. Participants will complete these procedures at home. A reminder to complete the procedures will be included in the drug diary.

5.3.8 Week 6, Visit 4 –End of Study Procedures: (+/- 2 days)

Visit 4, Week 6 procedures will be conducted over four days. The visit will include one day as outpatient visit to the MRCU for the meals (as was done in visit 1) and three days inpatient days, with participants staying overnight for 2 nights in the inpatient unit. The one outpatient visit to the MRCU will be performed within the 2 days prior to prior to the inpatient admission. The below evaluations can be performed within these 4 days:

- MCRU meals and assessments within 2 days prior to inpatient admission. Dietary and exercise assessment may be conducted on this day, if this is more conducive to the subject's and research team's schedule.
- Diet and Exercise Assessment – collection and review of accelerometer and food record as well as weight and BMI measurement. The assessment may be conducted on the day that the participants come into the MCRU to pick up their metabolic diet.
- C-SSRS
- Q-Les-Q

- AE Assessment
- ECG
- Clinical Labs:
  - Electrolytes (Na, K, Cl, HCO_3)
  - Liver Function Tests (Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Direct Bilirubin)
  - CBC w/differential
  - Serum creatinine
  - BUN
  - urinalysis,
  - plasma glucose,
  - plasma insulin,
  - lipid profile: (Total Cholesterol, Triglycerides, HDL Cholesterol, LDL Cholesterol (calculated)),
  - Apolipoprotein panel
  - lipoprotein profile: Plasma lipid analysis, including VLDL, LDL and HDL particle size and number are measured by nuclear magnetic resonance (NMR) spectroscopy using the Vantera Clinical Analyzer (LipoScience Inc., Raleigh, North Carolina) in the Clinical Center. This clinical test quantifies VLDL-P, LDL-P and HDL-P based on lipoprotein particle size using the amplitudes of their distinct lipid methyl group NMR signals to calculate the different lipoproteins. Lipoprotein particles is further subdivided into large, medium, and small particles based on the mean particle sizes as the weighted average of related subclasses. Results of this test are reported in the CRIS electronic medical record system. The rationale for adding this test is that cyclic AMP (cAMP) signaling in the liver decreases lipid synthesis. Therefore, it is possible that roflumilast, by increasing cAMP and activating protein kinase A, may decrease hepatic lipid production.
  - C-peptide,
  - HbA1C,
  - free fatty acids (FFA),
  - highly sensitive C-reactive protein,
  - thyroid stimulating hormone function tests
  - Serum pregnancy test

Day 2 of Admission
- Assessment of hepatic insulin sensitivity
- Euglycemic clamp study
- Measurements of Brachial Artery Flow and Forearm Capillary Recruitment (if the research team was able to schedule any of these procedures)
- Measurement of Plasma Incretins, circulating inflammatory markers and adipocytokines
- PBMC collection
- Research Blood Samples for Future Biochemical Studies

Day -2/-1 or Day 1/3:
- Radiologic Assessments
  - DEXA

Day -2/-1 or Day 1:
  - MRI and MRS (Assessment of visceral, liver, and skeletal muscle fat content

and distribution)

Day -2/-1 or Day 1:
- Optional Muscle biopsy
- Optional Adipose tissue biopsy
- Pill count and review of study drug diary (Day 1, 2, or 3)

Day 3 (Day of discharge)
- Mixed Meal Stimulation Test
- Radiological assessment (if not obtained earlier)

5.3.9 Week 7, Visit 5- Follow-up visit procedures (+/- 2 days)

The following procedures will be performed at this visit.
- AE evaluation
- Weight will be measured

5.3.10 General Procedure Considerations for each study visit

5.3.10.1 Medical History and Physical Examination

Medical history (including medication history involving over-the-counter and herbal medications), physical examination, and laboratory values will be completed on each subject for every admission while on the study. Vital signs and biophysical data (including blood pressure, heart rate, respiratory rate, temperature, height, and weight) will also be collected at each visit. These measurements will be made per NIH Clinical Center inpatient protocols.

5.3.10.2 Laboratory Tests and Parameters

Any laboratory test result that the Investigator considers clinically significant will be repeated at the discretion of the investigator to rule out laboratory error. For tests where a persistent abnormality is considered to be drug related, repeat analyses will be performed until the cause is determined and either a return to normality occurs or the investigator deems the abnormality to be of no clinical significance. Any values judged by the investigator to represent a clinically significant, abnormal change from baseline during the treatment phase will be recorded as an adverse event. Per Clinical Center policy, no more than 550 mL of blood will be collected over an 8-week period.

5.3.10.3 Procedures

All tests will follow NIH Clinical Center policies and clinical consent forms for individual tests requiring these will be obtained in addition to the study protocol consent. Sedation for tissue biopsy sampling will be offered in accordance with Clinical Center policies. Indicated and recognized pharmacologic compounds that are routinely employed to increase the sensitivity and specificity of certain tests may be employed in these tests in compliance with Clinical Center policies. With the exception of the pregnancy test, any of the listed procedures or laboratory tests performed within 4 weeks prior to screening visit in this protocol may/may not be repeated. However, if these procedures are not repeated, the prior studies (within the last 4 weeks) will be reviewed in CRIS as part of the protocol. If data from another Clinical Center protocol is used, this will be clearly documented in the source document. The purpose for not repeating study procedures is to prevent unnecessary

inconveniences, risks or discomforts for study participants. The investigator will determine based on the scientific objectives of the protocol as well as participant safety, which results will be used.

5.3.10.4 Off Treatment and Off Study Procedures

Participants taken off treatment due to serious adverse events, such as liver toxicities (elevated AST/ALT and bilirubin), major depression, suicidal ideation, and/or >10% weight loss, will be monitored to verify that the appropriate interventions are performed and until the event resolves in severity to baseline, at which time they will be taken off study.

Participants may opt to discontinue treatment at their request. The risks of opting to discontinue treatment will be discussed, and we will request permission to follow-up with the participant for one more week to ensure patient safety and well-being.

Participants who request going off study on their own accord will be queried as to why they are withdrawing, and we will request permission to follow-up with the participant for one additional week to ensure patient safety and then take them off study.

5.4 Schedule of Events

	Screening	Visit 1 (Days -2, or -1); Day1, 2,3)	Visit 2 (Wk2/ Day 15) (+/-2 days)	Visit 3 (Wk3/ Day 22) (+/- 4 days)	Week 5	Visit 4 (Wk6/ Days 42) (+/-2 days)	Visit 5 (Wk7) (+/- 2 days)
General Assessments							
informed Consent	**X**						
medical history	**X**						
physical examination	**X**						
electrocardiogram	**X**			**X**		**X**	
Psychiatric Evaluations							
C-SSRS	**X**					**X**	
SCID	**X**						
Q-Les-Q	**X**					**X**	
Diet and Exercise Assessment							
MCRU Meals		**X**				**X**	
3-Day Food Records	**X**	**X**			**X**	**X**	
Accelerometer	**X**	**X**			**X**	**X**	
collection and review of accelerometer and food record		**X**				**X**	
Weight and/or BMI	X	**X**	**X**	**X**		**X**	**X**
Drug Administration							
Dispensing of Medication		**X** [B]	**X**				
Observation of 1st dose		**X** [B]					
Dose Escalation			**X**				
Pill count/study diary review			**X**	**X**		**X**	
Adverse Event Assessment							
Assessment		**X** [B]	**X**	**X**		**X**	**X**

	Screening	Visit 1 (Days -2, or -1); Day1, 2,3)	Visit 2 (Wk2/ Day 15) (+/-2 days)	Visit 3 (Wk3/ Day 22) (+/- 4 days)	Week 5	Visit 4 (Wk6/ Days 42) (+/-2 days)	Visit 5 (Wk7) (+/- 2 days)
Clinical Lab tests							
CBC w/ differential	**X**	**X**				**x**	
Electrolytes [Sodium (Na), Potassium (K), Chloride (Cl), Bicarb (HCO3)]	**X**	**X**		**X**		**X**	
Liver Function Tests [Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Direct Bilirubin]	**X**	**X**		**X**		**X**	
Serum creatinine	**X**	**X**		**X**		**X**	
BUN	**X**	**X**		**X**		**X**	
plasma glucose	**X**	**X**				**X**	
plasma insulin	**X**	**X**				**X**	
Lipid profile [Total Cholesterol, Triglycerides, HDL Cholesterol, LDL Cholesterol]	**X**	**X**				**X**	
Plasma lipid analysis (lipoprotein profile, apolipoprotein panel)		**X**				**X**	
C-peptide	**X**	**X**				**X**	
free fatty acids (FFA)	**X**	**X**				**X**	
highly sensitive C-reactive protein	**X**	**X**				**X**	
Hemoglobin A1C (HbA1C)	**X**	**X**				**X**	
Thyroid Function Test	**X**					**X**	
Anti-HIV-1/2	**X**						
Anti-HCV Antibody	**X**						

	Screening	Visit 1 (Days -2, or -1); Day1, 2,3)	Visit 2 (Wk2/ Day 15) (+/-2 days)	Visit 3 (Wk3/ Day 22) (+/- 4 days)	Week 5	Visit 4 (Wk6/ Days 42) (+/-2 days)	Visit 5 (Wk7) (+/- 2 days)
Anti-HBc (Total IgG and IgM)	X						
Urinalysis	X	X				X	
Serum Pregnancy[C]	X	X		X		X	
Other Laboratory Assessments							
Assessment of hepatic insulin sensitivity		X [A]				X	
Glucose clamp		X [A]				X	
Mixed Meal Stimulation Test		X [B]				X	
Plasma incretin, adiponectin, leptin, adhesion molecules, TNF-α, & MCP-1 levels		X [A]				X	
PBMC collection		X				X	
Radiologic Assessments:							
DEXA		X [A]				X	
MRI/MRS (Assessment of visceral, liver, and skeletal muscle fat content and distribution)		X [A]				X	
Vascular Function by Ultrasound		X				X	
Optional Biopsy Assessments							
muscle biopsy		X [A]				X	
Adipose Tissue		X [A]				X	
Research Samples							
Blood Samples for Future Biochemical Studies		X [D]				X	

	Screening	Visit 1 (Days -2, or -1); Day1, 2,3)	Visit 2 (Wk2/ Day 15) (+/-2 days)	Visit 3 (Wk3/ Day 22) (+/- 4 days)	Week 5	Visit 4 (Wk6/ Days 42) (+/-2 days)	Visit 5 (Wk7) (+/- 2 days)
[A] These assessments can be performed on either on the outpatient visit just prior to admission or during 1st day of admission of visit 1, with the exception of DEXA which can also be performed on Day 3 of admission **[B] These assessments will be performed on third inpatient day of visit prior to release from the clinical center** **[C] May be performed at any time pregnancy is suspected.** **[D] This assessment can be performed on either the first or second inpatient day of Visit 1**							

VISIT #1 and #4 - SAMPLE INPATIENT VISITS

Day -1 or Day -2 prior to admit	Inpatient Day 1	Inpatient Day #2	Inpatient Day #3
Pick up metabolic meals MRI/MRS (if subject cannot be scheduled as inpatient) DEXA (if subject cannot get as inpatient) Optional: Muscle or adipose biopsy (for subjects who consent)	Metabolic diet Collection of food diary and accelerometer Admission to inpatient metabolic unit at 2 PM. Assessment of venous access; History and physical Metabolic meal DEXA (if not done on Inpatient Day #3) Optional: Muscle & adipose biopsy MRI/MRS (if subject cannot be scheduled as inpatient)	PBMC collection, 10 mL blood for future research, clinical lab collection Glucose tracer study (takes approximately 6 hours) Glucose clamp (takes approximately 3 hours) Doppler Ultra Sound and Brachial artery test at bedside during clamp	DEXA (if not done on Inpatient Day #1) Mixed meal test Drug dispensing, then observe for 2 hours (for visit 1 only) Discharge home.

6 Pharmaceuticals

6.1 Roflumilast

- **Other names:** DALIRESP® in US
- **Classification:** Selective phosphodiesterase 4 (PDE4) inhibitor
- **Route of Administration:** Oral
- **Roflumilast Dose**
  The dose (500 mcg once daily) was chosen based on double-blind, randomized parallel-group study that showed roflumilast administration for 12 week decreased blood glucose and HbA1c levels in patients aged 35-70 years with newly diagnosed type 2 diabetes who were treatment naïve when compared with placebo. However, due to gastrointestinal side effects associated with the 500 mcg dose, we will start with 250 mcg once daily for the first two weeks before increasing the dose to 500 mcg once daily for 4weeks.

Drug Supply:

- Roflumilast will be obtained from commercial sources as a 500mcg tablet. Patients will take: 250 mcg (one-half tablet) daily for 14 days, followed by 500 mcg (1 tablet) daily for 4 weeks
- **Stability/Storage:** Controlled Room Temperature at 20-25 C (68-77 F); excursions permitted to 15-30C (59 – 86 F).
- **Regulatory Status**:
  On February 28, 2011 the FDA approved Forest Research Institute, Inc.'s New Drug Application (N022522) for roflumilast, 500mcg tablets, for the treatment of COPD. An IND determination request was submitted to the FDA and the FDA issued a letter, included with submission, on April 19, 2012 stating the use of roflumilast in this study is exempt from IND requirements as stated in 21 CFR 312.2 (b) (1) (i-v). Specifically, the use is exempt because:
  1. The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use, nor intended to be used to support any other significant change in the labeling for the drug.
  2. The investigation is not intended to support a significant change in the advertising for a prescription drug product.
  3. The investigation does not involve a change in route of administration, dosage level, or patient population, or other factor that significantly increases the risks (or decreases the acceptability of risks) associated with use of the drug product.
  4. The investigation is conducted in compliance with the requirements for institutional review (21 CFR 56) and informed consent (21 CFR 50).
  5. The investigation is conducted in compliance with the requirements of 21 CFR 312.7, i.e., the drug may not be represented as safe or effective, nor may it be commercially distributed, for the purposes for which it is under investigation.

6.1.1 Dispensing Study Drug:

The NIH Pharmacy will dispense roflumilast medication in dosages of 250 mcg (one half tablet of 500mcg) and 500 mcg (one tablet) to the study participants.

6.1.2 Treatment Compliance monitoring:

Subjects will be prescribed and given the drug initially at the NIH Clinical Center. Treatment compliance will be monitored by reviewing the study drug diary. Participants will instructed to complete the medication diary each day at the time they take the study drug. Patients with questions regarding any adverse effects will have access to trained medical staff including the study nurse and physician at all times. Records of follow-up contact to verify subject compliance with drug intake will also be documented in the individual research chart.

Participants will return any unused roflumilast tablets at the completion of each visit. At this time a pill count will be performed and the study drug diary will be reviewed.

In instances where a subject misses a dose, the subject will be instructed to take the study drug as soon as he/she remembers. If it is almost time for the next dose, subjects will be instructed to skip the missed dose and take the medicine at the next regularly scheduled time. Extra medicine should not be taken to make up the missed dose. Follow-up phone calls may be placed as often as daily while the subject is on study drug. If subjects become unable or unwilling to continue treatment they will be removed from the study. The subjects will be instructed to return remaining drug, in original drug containers, to NIH at each applicable study visit for a drug count, or if all the drug has been taken, empty drug containers will be returned. Any missed doses of the study drug will be returned to the NIH pharmacy for disposal.

6.2 Stable isotope compound: 6,6 D2-Glucose

Drug Supply: Pine Pharmaceutical Company

6.2.1 Dispensing Study Drug:

The NIH Pharmacy will dispense the stable isotope compound to the study investigators.

7 Data Collection and Management Plan

Research Samples for Future Use- Before the beginning of each glucose clamp study, the subjects will have 10 ml blood drawn to be stored so that determination of plasma analytes that are not currently anticipated may be made. Additionally, the expression levels of the PGC-1a, PGC-1b, UCP, MCAD, ERRa genes may be measured. These samples are immediately centrifuged for 5 minutes at 3,000 rpm in a clinical centrifuge and the plasma collected and stored at -80˚C. Until the final analysis is completed for this protocol, samples will be coded with access to the sources kept in a security protected database, protected. When data analysis has been completed, the code will be stripped of all identifiers by use of an arbitrary or random alphanumeric code and the key to the code will be destroyed, thus making it impossible for anyone to link the samples to the sources. The NHLBI IRB will be notified in writing when this is done.

Data will be kept on the NHLBI "P" drive, accessible through password-protected computers. Only the members of the research team will have access to the samples and data.

All human subjects personally identifiable information (PII) as defined in accordance to the Health Insurance Portability and Accountability, eligibility and consent verification will be recorded in DIR's Clinical Data System (CDS) database. Primary data obtained during the conduct of the protocol will be kept in secure network drives that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual participant.

At the completion of the protocol (termination), samples and data will either be destroyed, or after IRB approval, transferred to another existing protocol or a repository.

End of study procedures: Data will be stored in locked cabinets and in a password protected network

servers until it is no longer of scientific value.

Loss or destruction of data: Should we become aware that a major breech in our plan to protect subject confidentiality and trial data has occurred, the IRB will be notified.

Publication Policy: Investigators will publish and present the results of the study. In all publications and presentations resulting from this research project the anonymity of the research subjects will be protected.

Privacy and Confidentiality: All efforts, within reason, will be made to keep subjects' protected health information (PHI) private. Using or sharing ("disclosure") such data must follow federal privacy rules. Under certain circumstances, the United States Office of Human Research Protections (OHRP) and the NHLBI Institutional Review Board (IRB) will be able to inspect and copy confidential study-related records which identify participants by name. Therefore, absolute confidentiality cannot be guaranteed. Authorized personnel from NIH, NHLBI, NIDDK, the NHLBI IRB, or other appropriate authorities, may have access to our research files in order to verify that the rights of the research subjects have been safeguarded.

Transmission of Data to Outside Investigators: Data will not be sent outside NIH without IRB notification and an executed agreement.

8 Statistical Considerations

8.1 Statistical Methods

For this exploratory study, primary and secondary outcomes will be considered significant at $p<0.05$. All tests will be two-sided. Differences from baseline to the end of 6weeks in the outcome measures will be evaluated using paired t-tests and linear regression if additional variables are needed in the models. Data will be checked for normality and appropriate transformations will be applied if necessary. Nonparametric analysis methods will be performed if needed.

Normality in the response variable will be assessed using the Shapiro-Wilk statistic and normal probability plots. Tukey's re-expression ladder will be used to identify transformations such that the relationships between the response and the covariates are linear. Non-parametric tests, such as the Wilcoxon Signed Rank test for paired data and the Mann-Whitney (Wilcoxon Rank Sum) test for unpaired data, will be used in place of the paired and unpaired Student t-tests, respectively, if the normality assumption of the data is in question.

8.2 Sample Size Calculation

The primary outcome in this study is changes in insulin sensitivity as measured by glucose clamp. Insulin sensitizing interventions such as weight loss and pharmacotherapy, improve insulin-mediated glucose disposal by 10~30% or more. Based on mean values of insulin sensitivity using the clamp method, a sample size of n=15 will be sufficient to detect a 20% difference pre- and post-treatment with 80% power (alpha = 0.05, 2-sided test, with SD change of 2.5 units)(Magkos, F et alInt J Obes (Lond). 2011 September; 35(9): 1233–1240). A 20% difference was chosen because it represents a clinically meaningful difference that is expected based on published data with other insulin sensitizing interventions, such as weight loss and pharmacotherapy. The Power Tables below indicate the minimal required sample size to be 12 to cover the most hypotheses.

**** Power Table ****

mean.null	***sd1***	***mean.alt***	***delta***	***alpha***	***power***	***n1***

0	*2.5*	*2*	*2*	*0.05*	*0.8*	*12*

*** Power Table ***

mean.null	***sd1***	***mean.alt***	***delta***	***alpha***	***power***	***n1***
0	*2.5*	*2.2*	*2.2*	*0.05*	*0.8*	*11*

*** Power Table ***

mean.null	***sd1***	***mean.alt***	***delta***	***alpha***	***power***	***n1***
0	*2.5*	*2.4*	*2.4*	*0.05*	*0.8*	*9*

We propose to have a recruitment ceiling of 50 subjects in order to obtain n = 15. This allows for a drop-out rate of 20%.

9 Data and Safety Monitoring

9.1 Safety Monitoring

Accrual and safety data will be monitored by the Principal Investigator who will provide oversight to the conduct of this study.

Accrual and safety data will be monitored and reviewed annually by the Institutional Review Board (IRB). Prior to implementation of this study, the protocol and the proposed subject informed consent document will be reviewed and approved by the properly constituted IRB operating according to the 45 CRF 46 and 21 CFR 56. This committee must approve all amendments to the protocol or informed consent document, and conduct continuing annual review so long as the protocol is open to accrual or follow up of subjects.

9.2 Adverse Event Characterization and Reporting

9.2.1 Definitions

Adverse Event (AE): Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the research.

Serious Adverse Event (SAE): A serious adverse event that:

- results in death;
- is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- results in in-patient hospitalization or prolongation of existing hospitalization;
- results in a persistent or significant incapacity;
- results in a congenital anomaly/birth defect; or
- based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Suspected adverse reaction: Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Unexpected adverse reaction: An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the package insert or is not listed at the specificity or severity that has been observed; or is not consistent with the risk information described in the protocol or elsewhere in the current application. "Unexpected", also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs

or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Unanticipated Problem (UP): Any incident, experience, or outcome that is:

1. unexpected in terms of nature, severity, or frequency in relation to
   a. the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents; and
   b. the characteristics of the subject population being studied; and
2. related or possibly related to participation in the research; and
3. places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Unanticipated Problem that is not an Adverse Event: An unanticipated problem that does not fit the definition of an adverse event, but which may, in the opinion of the investigator, involves risk to the subject, affect others in the research study, or significantly impact the integrity of research data. For example, report occurrences of breaches of confidentiality, accidental destruction of study records, or unaccounted-for study drug.

Protocol Deviation (PD): Any change, divergence, or departure from the IRB approved study procedures in a research protocol that does not have a major impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.

9.2.2 Adverse Event Recording

The principal investigator (and medical advisory investigator) will be responsible for assessing adverse events. Information on adverse events will be solicited from subjects through questions from study personnel and information volunteered by the subject. All patients will be specifically counseled to report physical symptoms or changes experienced while on treatment. Inquiries will be made to subjects at least once every 7 days to inquire about potential adverse effects. Liver function tests will be performed at visit 3, and 4 after the initiation of roflumilast.

Adverse event recording will start after the initial dose of the drug is administered.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be recorded and followed until satisfactory resolution. AEs should be reported up to the end of the subject's participation in the study. AEs that are considered treatment related, expected, continuing, but not resolvable by the end of the subject's participation in the study will not be followed after the end of the subject's participation in the study.

An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

The intensity of adverse events will be graded as follows:

Mild: Awareness of sign or symptom, but easily tolerated. Not expected to have a clinically significant effect on the patients overall health and well-being. Not likely to require medical attention.

Moderate: Discomfort enough to cause interference with usual activity or affects clinical status. May require medical intervention.

Severe: Incapacitating or significantly affecting clinical status. Likely requires medical intervention and/or close follow-up.

9.2.3 Event Reporting

Reporting Timeframes to IRB Chair, Clinical Director, and/or NHLBI IRB

Serious Events

Reports to the IRB and CD: The PI must report Serious UPs, and Serious PDs to the IRB and CD as soon as possible but not more than 7 days after the PI first learns of the event using the NIH Problem Report Form.

Reports to the IRB Chair and CD: The PI must report all SAEs that do not meet the definition of UP to the IRB chair and CD not more than 14 days after the PI first learns of the event, using the SAE submission form.

Non-serious Events

Reports to the IRB and CD: The PI must report all UPs that are not Serious to the IRB and CD, and PDs that are not Serious to the IRB, not more than 14 days after the PI first learns of the event using the NIH Problem Report Form.

Deaths

The PI must report all deaths (that are not UPs) to the CD as soon as possible, but not more than 7 days after the PI first learns of the event.

We request a waiver from reporting the following commonly occurring, mild to moderate, and expected events to the IRB unless they reach the threshold of an SAE, at which time these events will also be reported to the IRB as UP:

- Emergence or worsening of insomnia, anxiety, weight loss of < 10% of baseline total body weight
- Bruising and possible inflammation at intravenous catheter sites
- Nausea with emesis or headache
- Symptoms specifically mentioned in the consent form that do not threaten patient safety.
- Asymptomatic correctable hypoglycemia

The following adverse events will be listed in the consent and reported to the IRB at the time of continuing review:

- Subject withdrawal from study before completion related to intolerance of medication regime or other non-serious adverse events
- Suicidal ideation and new onset depression.

- moderate weight loss (≥ 10% of baseline total body weight)

9.3 Stopping Rules

Monitoring of Subjects and Criteria for Withdrawal of Subjects

Participants may choose to withdraw from this study at any time for any reason. Participants who withdraw will be compensated for their time per guidelines stated in this protocol. Participants will be withdrawn from the study if they cannot continue with the study regimen or: a) develop major depression or suicidal ideation, b) if there is suspected hypersensitivity to the study medication; or c) develop significant weight loss (> 10% of initial body weight), or c) die. If serum transaminases (ALT/AST) or bilirubin exceed 3 times the upper limit of normal and/or if clinical signs and symptoms suggest the onset of hepatic dysfunction, participants will be withdrawn from the study and treatment discontinued. Participants will be followed until the resolution of abnormalities with appropriate medical management. Participants who become pregnant or diabetic during the study will be withdrawn and referred to their primary care doctor.

Criteria for suspending study
If 2 out of 15 participants experience major depression or suicidal ideation serious adverse events, recruitment and randomization will be suspended to determine if after review of the data, the study should be stopped. The IRB will be informed if this occurs.

9.4 Protocol Monitoring

As per ICH-GCP 5.18 clinical protocols are required to be adequately monitored by the study sponsor. The Principal Investigator and/or designee will have primary responsibility for monitoring the clinical trial data.

The investigator (and/or designee) will make study documents (e.g., consent forms and pertinent hospital or clinical records readily available for inspection by the local IRB, the site monitors, and the NHLBI staff for confirmation of the study data.

10 Human Subjects Protections

10.1 Rationale for Subject Selection

Subjects of both genders will be considered for inclusion in this study. There will be no racial, ethnic, or gender discrimination. Presence of metabolic dysfunction and insulin resistance is firmly established in all races and genders. Therefore, it is appropriate to study the effects of roflumilast to modulating insulin resistance and pancreatic β-cell function in these populations. Cognitively impaired and institutionalized persons will not participate in this study. Criteria for exclusion or withdrawal from the study are based on the presence of other disease processes that may be harmful to the health of subjects.

10.2 Rationale for the Exclusion of Children

Subjects under 18 years of age will not be considered for inclusion in this protocol because roflumilast is not approved for use in children and there is no direct medical benefit from participation in this study.

10.3 Rationale for the Exclusion of Pregnant Women

The effects of roflumilast on pregnant women have not been evaluated to date in a controlled clinical trial. Thus, given this and the lack of known direct medical benefit to participants of this study, pregnant women will be excluded from the study.

10.4 Risk/Benefit Assessment

There are no direct benefits for the subjects participating in this study although information obtained may help to establish the health benefits of roflumilast for subjects with prediabetes. In addition, the screening physical exam and laboratory tests may provide information that is useful for the subjects. Abnormal values will be discussed with the study volunteers and forwarded to their primary care physicians.

The level of risk to the adult research participants is greater than minimal risk and involves no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge to further society's understanding of the disorder or condition under study. This assessment is in accordance with 45 CFR 46.102 (h)(i).

As of June 28, 2017, this study is closed to accrual, and is now in data and/or sample analysis only. Therefore, the level of risk is now minimal.

10.5 Risks and Discomforts

10.5.1 Roflumilast-related toxicity:

AdverseReactionsReportedby≥2%ofPatients
TreatedwithroflumilastmcgdailyandGreaterThanPlacebo

	Treatment	
Adverse Reactions (Preferred Term)	**DALIRESP** (**N**=4438) **n (%)**	**Placebo** (**N**=4192) **n (%)**
Diarrhea	**420(9.5)**	**113 (2.7)**
Weight decreased	**331 (7.5)**	**89 (2.1)**
Nausea	**209 (4.7)**	**60 (1.4)**
Headache	**195 (4.4)**	**87 (2.1)**
Back pain	**142 (3.2)**	**92 (2.2)**
Influenza	**124 (2.8)**	**112 (2.7)**
Insomnia	**105 (2.4)**	**41 (1.0)**
Dizziness	**92 (2.1)**	**45 (1.1)**
Decreased appetite	**91 (2.1)**	**15 (0.4)**

Adverse reactions that occurred in the roflumilast group at a frequency of 1 to 2% where rates exceeded that in the placebo group include:

- Gastrointestinal disorders - abdominal pain, dyspepsia, gastritis, vomiting
- Infections and infestations - rhinitis, sinusitis, urinary tract infection,
- Musculoskeletal and connective tissue disorders - muscle spasms
- Nervous system disorders - tremor
- Psychiatric disorders - anxiety, depression

Psychiatric Events including Suicidality:
Treatment with roflumilast is associated with an increase in psychiatric adverse reactions. In 8 controlled clinical trials 5.9% (263) of patients treated with roflumilast 500 mcg daily reported psychiatric adverse reactions compared to 3.3% (137) treated with placebo. The most commonly reported psychiatric adverse reactions were insomnia, anxiety, and depression which were reported at higher rates in those treated with roflumilast 500 mcg daily (2.4%, 1.4%, and 1.2% for roflumilast versus 1.0%, 0.9%, and 0.9% for placebo,

respectively) [see [package insert] Adverse Reactions (6.1)]. Instances of suicidal ideation and behavior, including completed suicide, have been observed in clinical trials. Three patients' experienced suicide-related adverse reactions (one completed suicide and two suicide attempts) while receiving roflumilast compared to one patient (suicidal ideation) who received placebo.

Weight Decrease

Weight loss was a common adverse reaction in roflumilast clinical trials and was reported in 7.5% (331) of patients treated with roflumilast 500 mcg once daily compared to 2.1% (89) treated with placebo Adverse Reactions (6.1)]. In addition to being reported as adverse reactions, weight was prospectively assessed in two placebo-controlled clinical trials of one year duration. In these studies, 20% of patients receiving roflumilast experienced moderate weight loss (defined as between 5-10% of body weight) compared to 7% of patients who received placebo. In addition, 7% of patients who received roflumilast compared to 2% of patients receiving placebo experienced severe (>10% body weight) weight loss. During follow-up after treatment discontinuation, the majority of patients with weight loss regained some of the weight they had lost while receiving roflumilast. Patients treated with roflumilast should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated, and discontinuation of roflumilast should be considered.

10.5.2 Glucose clamp study:

The major potential risk in this study is the development of hypoglycemia during the glucose clamp studies. This is extremely unlikely because blood glucose levels are monitored at 5 to 10 minute intervals throughout the study and for at least one hour after the insulin infusion has been stopped. Venous access is available to give appropriate glucose infusions should significant hypoglycemia occur. The YSI glucose analyzer we use meets CLIA requirements for Quality Assurance in patient testing. The administration of insulin can theoretically result in low blood glucose. With low blood glucose, people get hungry, have a headache, feel shaky or dizzy or may become drowsy or sweat. If low blood glucose does occur, the test will be stopped and the subject will be given juice or glucose by vein to raise the blood glucose to normal. Hypokalemia is avoided by establishing baseline potassium levels before starting the study and monitoring during and at the completion of the insulin infusion. A potassium phosphate infusion is given during the glucose clamp procedure to maintain serum potassium levels in the normal range. The Clinical Pathology Laboratory at NIH gives results within 15 minutes for monitoring of patient serum potassium levels.

10.5.3 Dual Energy X-ray absorptiometry (DEXA):

Although DEXA is a safe procedure, it is associated with a small amount of ionizing radiation. The radiation exposure is less than 0.3.0mrem per study, for total exposure of 0.6.0mrem. In some subjects, lying on the table may result in some discomfort due to back pain or claustrophobia.

ORGAN	RADIATION DOSE (rem)		
	Per single Administration	ICRP 103 weighting factor	Per Year (12 mos.)
Adrenals			
Brain			
Breasts			
Esophagus [1]			
Gallbladder Wall			
GI-tract: Lower Large Intestine			
Small Intestine			
Stomach			
Upper Large Intestine			
Colon [2]			
Heart Wall			
Kidneys			
Liver			
Lungs			
Muscle			
Ovaries			
Pancreas			
Red Marrow			
Bone Surfaces			
Skin	0.3	0.01	0.6
Spleen			
Testes			
Thymus			
Thyroid			
Urinary Bladder Wall [3]			
Lens of Eye			
Uterus			
REMAINDER AVE			
EFFECTIVE DOSE	**0.003**	0.01	**0.006**

NOTES:

[1] Since no dose is explicitly tabulated for esophagus, thymus dose is used (as per ICRP 80)

[2] Colon Dose estimated by [0.57 ($Dose_{ULI}$) + 0.43 ($Dose_{LLI}$)] (as per ICRP 80).

[3] Dynamic urinary bladder model used; void interval of **___ hours**

DOSIMETRY SOURCE: Lunar iDXA Safety and Technical Specifications Manual GE Healthcare LUNAR

enCORE iDXA Safety and Specification Manual Draft Sept

Lunar enCORE Systems

	iDXA
Mode	**Patient thickness**
Thick	>25 cm
Standard	13-25 cm
Thin	<13 cm

Current and typical dose information for Lunar iDXA modes

Site	Mode[1]	Current (mA)[2]	Typical Measurement Area L x W cm x cm[4,5]	Irradiation times (sec)[3,4,5]	Estimated Skin Entrance Dose (µGy)[6,7]
AP Spine	Thick	2.500	19.0 x 18.0	104	329
AP Spine	Standard	2.500	19.0 x 18.0	50	146
AP Spine	Thin	0.625	19.0 x 18.0	12.5	37
Femur	Thick	2.500	20.5 x 17.0	106	329
Femur	Standard	2.500	20.5 x 17.0	52	146
Femur	Thin	0.625	20.5 x 17.0	13	37
DualFemur	Thick	2.500	2 x 20.5 x 17.0	212	329
DualFemur	Standard	2.500	2 x 20.5 x 17.0	104	146
DualFemur	Thin	0.625	2 x 20.5 x 17.0	26	37
Total Body	Thick	0.188	194.5 x 66.0	55.6	6
Total Body	Standard	0.188	194.5 x 66.0	30.5	3
Total Body	Thin	0.188	194.5 x 66.0	30.5	3
LVA	Standard	2.500	39.3 x 18.0	214	329

[1] All modes are 100kV, ±1kV.
[2] Tube current is ±1% at the maximum current.
[3] Imaging time measured from shutter open to shutter close, 90% to 100% of indicated value.
[4] Sizes of measurement areas and irradiation times will be less than those listed above if you use the SmartScan feature.
[5] Measurement lengths and times are dependent on patient height. The values shown are for a patient 168 cm (66 inches) tall who was measured without using SmartScan.
[6] Dose measurements are constrained by Daily QA limits.
[7] Irradiation times and dose values do not consider a "sweep retry" feature which can double the dose for a single transverse sweep within an entire scan. If a retry occurs a slight increase in irradiation time and skin entrance dose would be expected. The retry feature reduces need to rescan entire patient.

10.5.4 MRI/MRS assessment of visceral, liver and muscle fat:

There are no long-term risks or consequences of MRI/MRS scans without gadolinium contrast in patients. In the 3T scanner, it is possible that the patient may experience

peripheral nerve stimulation resulting in a sensation of mild twitching, warmth or vibration. The duration of the study is 90 minutes to 2 hours during which the subject will need to lie on the table. The tight space may prohibit patients of a particular body habitus to participate and may cause claustrophobic symptoms in susceptible individuals.

10.5.5 Blood drawing:
The placement of intravenous catheters may cause transient pain and bruising and rarely infection at the insertion site or phlebitis.

10.5.6 Stable isotopes:
The stable isotopes, deuterium is not associated with toxicity or abnormalities in metabolism.

10.5.7 Psychiatric Evaluations:
Participants may experience psychological discomfort or distress when answering questions pertaining to suicide, depression, quality of life, and their mental health in general.

10.5.8 Biopsy:
The major risks/discomforts include pain, bruising, hematoma, infection, scarring, and localized lipodystrophy. The degree of obesity will not add to the risk of this procedure. The procedure will be performed under sterile technique to minimize the chances of infection. Local anesthetic will be used to minimize pain. Ice will be applied to the site immediately after the procedure to limit bruising, swelling and tenderness. After subcutaneous tissue biopsy, patients will be monitored by nurses. Post-biopsy the incision site will be cleaned and closed with adhesive wound closures and covered with gauze and translucent dressing tape. Study participants will be instructed to report to the clinical staff any changes at the biopsy site including bleeding, secretion, erythema, pain, and signs and symptoms of infection. Study participants will be instructed to self-monitor the incision site after discharge from the Clinical Center.

10.5.9 Dietary assessments:
Participants may find the wearing the accelerometer for 3 days prior to each visit uncomfortable. Participants may not like the meals they are asked to eat. Participants may find writing down everything she/he eats for 3 days prior to each visit time consuming and bothersome.

10.5.10 Microbubble contrast administration:
Contrast agents have very few side effects in most people. Minor side effects occur in 5-8% of subjects and include headache, nausea, flushing and dizziness. These symptoms are usually short lived and do not require treatment. Allergic reactions have been seen with contrast agents, but they are very rare. In October 2007, the FDA issued a warning about serious complications with the use of contrast in critically ill subjects and in those with severe lung disease. In July 2008, the FDA removed several of the contraindications after studies in thousands of subjects showed that the benefits from diagnostic information outweighed the risks even for subjects at high risk for complications.

Definity is approved by the FDA for use with echocardiography for the purpose of endocardial definition and opacification of the left ventricle. It will be used in this study as an off-label investigational use of a marketed drug. According to the FDA website,

http://www.fda.gov/RegulatoryInformation/Guidances/ucm126486.htm the clinical investigation of a marketed drug does not require submission of an IND if all six of the following conditions are met:

i. it is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug *[correct]*
ii. it is not intended to support a significant change in the advertising for the product *[correct]*
iii. it does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product *[It will be given intravenously; there should be no change in the risk profile. Our collaborator, Dr. Lindner, has published extensively on this technique and has used microbubble agents with perfusion imaging for over 10 years with no evidence of increased risk.]*
iv. it is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively] *[correct]*
v. it is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR 312.7] *[not applicable]*
vi. it does not intend to invoke 21 CFR 50.24. *[This regulation refers to exception from informed consent requirements for emergency research and is not applicable to this study.]*

10.5.11 Brachial artery blood flow imaging:

There are no known risks to the ultrasound imaging.

10.6 Informed Consent Documentation

Each participant will receive an oral and written explanation of the goals, procedures, and risks of this study. The Principal Investigator and those Associate Investigators who are listed on the cover page of the protocol with an asterisk next to their name may obtain informed consent from research participants. Consent will be obtained at the NIH Clinical Center. The original, signed informed consent document will be placed in the medical record, and the subject will receive a signed copy of the informed consent document.

If there is an unexpected enrollment of a research participant for which there is no translated extant IRB approved consent document, the principal investigator and/or those authorized to obtain informed consent will use the Short Form Oral Consent Process as described in MAS Policy M77-2, 45 CFR 46.117 (b) (2). The summary that will be used is the English version of the extant IRB approved consent document.

We request prospective IRB approval of the use of the short form for up to a maximum of 5 participants in a given language and will notify the IRB at the time of continuing review of the frequency of the use of the Short Form. Should we reach the threshold of 5, we will notify the IRB of the need for an additional use of the Short Form and that we will have that consent document translated into the given inherent language.

10.7 Subject Advocate

A subject's rights representative is available to subjects on this protocol. The representative can be reached at 301-496-2626 and is located in Building 10. Subjects may ask any questions about the study and may withdraw their consent at any time.

11 Conflict of Interest

The National Institutes of Health reviews NIH staff researchers at least yearly for conflicts of interest. The following link contains details on this process http://ethics.od.nih.gov/forms/Protocol-Review-Guide.pdf.None of the members of the research team reported a potential conflict of interest.

12 Reimbursement for Travel

Reimbursement for local travel, US travel, food, and lodging will not be provided under this protocol.

13 Financial Compensation

There are no direct benefits for the subjects participating in this study although information obtained may help to establish the mechanism of action of roflumilast in overweight glucose-intolerant subjects. In addition, the screening physical exam and laboratory tests may provide information that is useful for the subjects. The screening visit will not be compensated but results of lab work will be made available to subjects and to their primary physician. Remuneration for participation in this study is based on existing NIH guidelines based on inconvenience, to offset potential loss of earnings and travel expenses. The amount paid will be prorated based upon participation. Participants may not participate in all tests and therefore an estimate of total potential compensation is not included. Participants will be compensated as described in the table below:

Description of tests or procedures	**Maximum Possible Compensation for each test**
1. Daily payment for visits. $50/day X 5maximum paid visits	$250
2. Mixed meal test (2 unit) ($50 x 2)	$100
3. Glucose clamp (2 unit) ($100 x 2)	$200
4. Ultrasound Imaging (2 Unit) (($50 x 2)	$60
5. Stable isotope studies (1 unit) ($30 x 2)	$100
6. DEXA Scan - Body composition (1 unit) ($50 x2)	$100
7. MRI/MRS Scan ($50 x2)	$100
8. Optional Muscle biopsy ($200 x 2)	$400
9. Optional Adipose Tissue biopsy ($50 x2)	$100
10. In patient ($40 x 4)	$160
Maximum possible compensation	$1570

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Appendix 1: Study drug Diary

DRUG DIARY		
Subject ID #:	**Protocol #:** 13-H-0123	**Protocol:** Roflumilast Effect on Insulin

INSTRUCTIONS:

There are 4 pages to the diary including the instructions on page 1. The diary pages have been written to correspond with Visits 2, 3, and 4. Page 2 is the page you will fill out between weeks 1 to the end of week 2, and you will need to bring it to Visit 2, at end of week 2. Page 3 is for week 3, and you will need to bring it to Visit 3, at end of week 3. Page 4 is for weeks 4 through week 6, and you will need to bring this page with you to Visit 4, at week 6.

(1) Number of Tablet of drug you must take by mouth each day:

- You must take by mouth ½ pill (that is, one half of a pill) of 500 mcg tablet once a day for the first 2 weeks or from Day 1 to Day 14.
- Then, you must take by mouth one 500 mcg tablets a day for the next 4 weeks or from Day 15 to Day 42.

(2) When you should take the roflumilast medication?

- You take the drug in the morning.
- If you forget to take the drug in the morning, take it later on that day as soon as you remember
- If you **MISS taking** the drug on any day while on study, **DO NOT TAKE extra tablets on the next day.**
- The drug can be taken before, with, or after a meal.

(3) Filling out the drug diary.

- Each day you take the drug, please write down the date, the number of tablets you take next to the Day #. For example, on Day 2, you will write the date in the second column and the number '1', for 1 tablet in the second column.
- You can also write down any comments you have about how the drug made you feel or if you forgot to take it in the last column.
- On pages 2, 3, and 4, there are 4 extra spaces at end of each diary. You will be given 4 extra days of tablets in case your next visit is not scheduled exactly at the end of weeks 2 and 6 of the study. These spaces can be used to write down when and the number of tablets you take if your visit is scheduled after the last day of week 2 and 6.

(4) If you have questions or are having problems while taking the drug or placebo, please call one of the following people:

- **Principal Investigator:** Dr. Jay Chung at 301-496-3075
- **Associate Investigator:** Dr. Ranganath Muniyappa at 301-451-7702
- **Research Nurse:** Sandra MacDonald, R.N. at 301-451-4899

DRUG DIARY		
Subject ID #:	**Protocol #:** 13-H-0123	**Protocol:** Roflumilast Effect on Insulin

Weeks 1 through 2 - Dates:_____

Day	Date	Number of Tablets Taken	Comments
Example	**1/1/2013**	**1**	**vomited hour later**
Day 1			Inpatient at NIH CC
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			
Day 8			
Day 9			
Day 10			
Day 11			
Day 12			
Day 13			
Day 14			

DRUG DIARY		
Subject ID #:	**Protocol #:** 13-H-0123	**Protocol:** Roflumilast Effect on Insulin

Week 3 Dates:_____

Day	Date	Number of Tablets Taken	Comments
Example:	**2/1/2013**	**2**	**vomited hour later**
Day 15			
Day 16			
Day 17			
Day 18			
Day 19			
Day 20			
Day 21			

DRUG DIARY		
Subject ID #:	**Protocol #:** 13-H-0123	**Protocol:** Roflumilast Effect on Insulin

Weeks 4 through 6 - Dates:_____

Day	Date	Number of Tablets Taken	Comments
Example:	**3/1/2013**	**2**	**vomited hour later**
Day 22			
Day 23			
Day 24			
Day 25			
Day 26			
Day 27			
Day 28			
Day 29			
Day 30			
Day 31			
Day 32			
Day 33			
Day 34			
Day 35			
Day 36			
Day 37			
Day 38			
Day 39			
Day 40			
Day 41			
Day 42			

Appendix 2: Columbia Suicide Severity Rating Scale

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

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SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - *Most Severe Ideation:* ____ *Type # (1-5)* _____ *Description of Ideation* Past X Months - *Most Severe Ideation:* ____ *Type # (1-5)* _____ *Description of Ideation*	Most Severe	Most Severe
Frequency *How many times have you had these thoughts?* (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration *When you have the thoughts how long do they last?* (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability *Could/can you stop thinking about killing yourself or wanting to die if you want to?* (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents *Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?* (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation *What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?* (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Lifetime	Past __ Years
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is *any* intent/desire to die associated with the act, then it can be considered an actual suicide attempt. *There does not have to be any injury or harm*, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. *Have you made a suicide attempt?* *Have you done anything to harm yourself?* *Have you done anything dangerous where you could have died?* *What did you do?* *Did you_____ as a way to end your life?* *Did you want to die (even a little) when you_____?* *Were you trying to end your life when you _____?* *Or Did you think it was possible you could have died from_____?* *Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?* (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. *Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?* If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. *Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?* If yes, describe:	Yes ☐ No ☐ Total # of aborted _____	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). *Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?* If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite availsble medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

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SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Lifetime: Time He/She Felt Most Suicidal

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?

Yes ☐ No ☐

If yes, describe:

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan.
Have you actually had any thoughts of killing yourself?

Yes ☐ No ☐

If yes, describe:

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."*
Have you been thinking about how you might do this?

Yes ☐ No ☐

If yes, describe:

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?

Yes ☐ No ☐

If yes, describe:

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?

Yes ☐ No ☐

If yes, describe:

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.

Most Severe

Most Severe Ideation: ____ _____

Type # (1-5) *Description of Ideation*

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day

____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous

____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts

____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply

____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain.
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply

____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is *any* intent/desire to die associated with the act, then it can be considered an actual suicide attempt. *There does not have to be any injury or harm*, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. *Have you made a suicide attempt?* *Have you done anything to harm yourself?* *Have you done anything dangerous where you could have died?* *What did you do?* *Did you_____ as a way to end your life?* *Did you want to die (even a little) when you_____?* *Were you trying to end your life when you _____?* *Or did you think it was possible you could have died from_____?* *Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?* (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes** ☐ **No** ☐ Total # of Attempts _____ **Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. *Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?* If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. *Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?* If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). *Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?* If yes, describe:	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

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SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Since Last Visit

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
Yes ☐ No ☐
If yes, describe:

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?
Yes ☐ No ☐
If yes, describe:

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."*
Have you been thinking about how you might do this?
Yes ☐ No ☐
If yes, describe:

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?
Yes ☐ No ☐
If yes, describe:

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
Yes ☐ No ☐
If yes, describe:

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe

Most Severe Ideation: ____ _____
Type # (1-5) *Description of Ideation*

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day
____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous
____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts
____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply
____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply
____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is *any* intent/desire to die associated with the act, then it can be considered an actual suicide attempt. *There does not have to be any injury or harm*, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes** ☐ **No** ☐ Total # of Attempts _____ **Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐
Suicide:	**Yes** ☐ **No** ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

Appendix 3:DALIRESP® package insert

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use DALIRESP safely and effectively. See full prescribing information for DALIRESP.

DALIRESP® (roflumilast) tablets
Initial U.S. Approval: 2011

----------INDICATIONS AND USAGE----------
DALIRESP is indicated as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. (1, 14)

Limitations of Use: DALIRESP is not a bronchodilator and is not indicated for the relief of acute bronchospasm. (1, 14)

----------DOSAGE AND ADMINISTRATION----------
The recommended dosage for patients with COPD is one 500 mcg tablet per day, with or without food. (2)

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 500 mcg (3)

----------CONTRAINDICATIONS----------
- Moderate to severe liver impairment (Child-Pugh B or C) (4)

----------WARNINGS AND PRECAUTIONS----------
- Acute bronchospasm: Do not use for the relief of acute bronchospasm. (5.1)
- Psychiatric Events including Suicidality: Advise patients , their caregivers, and families to be alert for the emergence or worsening of insomnia, anxiety, depression, suicidal thoughts or other mood changes, and if such changes occur to contact their healthcare provider. Carefully weigh the risks and benefits of treatment with DALIRESP in patients with a history of depression and/or suicidal thoughts or behavior. (5.2)
- Weight Decrease: Monitor weight regularly. If unexplained or clinically significant weight loss occurs, evaluate weight loss and consider discontinuation of DALIRESP. (5.3)
- Drug Interactions: Use with strong cytochrome P450 enzyme inducers (e.g. rifampicin, phenobarbital, carbamazepine, phenytoin) is not recommended. (5.4)

----------ADVERSE REACTIONS----------
Most common adverse reactions (≥ 2%) are diarrhea, weight decrease, nausea, headache, back pain, influenza, insomnia, dizziness and decreased appetite. (6.1)

To report SUSPECTED ADVERSE REACTIONS, Contact Forest Laboratories, Inc. at 1-800-678-1605 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Use with inhibitors of CYP3A4 or dual inhibitors of CYP3A4 and CYP1A2 (e.g, erythromycin, ketoconazole, fluvoxamine, enoxacin, cimetidine) will increase roflumilast systemic exposure and may result in increased adverse reactions. The risk of such concurrent use should be weighed carefully against benefit. (7.2)

----------USE IN SPECIFIC POPULATIONS----------
- Nursing Mothers: DALIRESP should not be used by women who are nursing as excretion of roflumilast and/or its metabolites into human milk is probable and there are no human studies that have investigated effects of DALIRESP on breast-fed infants. (8.3)

See 17 for PATIENT COUNSELING INFORMATON AND MEDICATION GUIDE

REVISED September 2011

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FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

DALIRESP® is indicated as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.

Limitations of Use

DALIRESP is not a bronchodilator and is not indicated for the relief of acute bronchospasm.

2 DOSAGE AND ADMINISTRATION

The recommended dose of DALIRESP is one 500 microgram (mcg) tablet per day, with or without food.

3 DOSAGE FORMS AND STRENGTHS

DALIRESP is supplied as white to off-white, round tablets, embossed with "D" on one side and "500" on the other side. Each tablet contains 500 mcg of roflumilast.

4 CONTRAINDICATIONS

The use of DALIRESP is contraindicated in the following conditions:

- Moderate to severe liver impairment (Child-Pugh B or C) [*see Clinical Pharmacology (12.3) and Use in Special Populations (8.6)*].

5 WARNINGS AND PRECAUTIONS

5.1 Treatment of Acute Bronchospasm

DALIRESP is not a bronchodilator and should not be used for the relief of acute bronchospasm.

5.2 Psychiatric Events including Suicidality

Treatment with DALIRESP is associated with an increase in psychiatric adverse reactions. In 8 controlled clinical trials 5.9% (263) of patients treated with DALIRESP 500 mcg daily reported psychiatric adverse reactions compared to 3.3% (137) treated with placebo. The most commonly reported psychiatric adverse reactions were insomnia, anxiety, and depression which were reported at higher rates in those treated with DALIRESP 500 mcg daily (2.4%, 1.4%, and 1.2% for DALIRESP versus 1.0%, 0.9%, and 0.9% for placebo, respectively) *[see Adverse Reactions (6.1)]*. Instances of suicidal ideation and behavior, including completed suicide, have been observed in clinical trials. Three patients experienced suicide-related adverse reactions (one completed suicide and two suicide attempts) while receiving DALIRESP compared to one patient (suicidal ideation) who received placebo.

Before using DALIRESP in patients with a history of depression and/or suicidal thoughts or behavior, prescribers should carefully weigh the risks and benefits of treatment with DALIRESP in such patients. Patients, their caregivers, and families should be advised of the need to be alert for the emergence or worsening of insomnia, anxiety, depression, suicidal thoughts or other mood changes, and if such changes occur to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment with DALIRESP if such events occur.

5.3 Weight Decrease

Weight loss was a common adverse reaction in DALIRESP clinical trials and was reported in 7.5% (331) of patients treated with DALIRESP 500 mcg once daily compared to 2.1% (89) treated with placebo [*see Adverse Reactions (6.1)*]. In addition to being reported as adverse reactions, weight was prospectively assessed in two placebo-controlled clinical trials of one year duration. In these studies, 20% of patients receiving roflumilast experienced moderate weight loss (defined as between 5-10% of body weight) compared to 7% of patients who received placebo. In addition, 7% of patients who received roflumilast compared to 2% of patients receiving placebo experienced severe (>10% body weight) weight loss. During follow-up after treatment discontinuation, the majority of patients with weight loss regained some of the weight they had lost while receiving DALIRESP. Patients treated with DALIRESP should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated, and discontinuation of DALIRESP should be considered.

5.4 Drug Interactions

A major step in roflumilast metabolism is the N-oxidation of roflumilast to roflumilast N-oxide by CYP3A4 and CYP1A2. The administration of the cytochrome P450 enzyme inducer rifampicin resulted in a reduction in exposure, which may result in a decrease in the therapeutic effectiveness of DALIRESP. Therefore, the use of strong cytochrome P450 enzyme inducers (e.g. rifampicin, phenobarbital, carbamazepine, phenytoin) with DALIRESP is not recommended. [*see Drugs That Induce Cytochrome P450 (CYP) Enzymes (7.1) and Clinical Pharmacology (12.3)*].

6 ADVERSE REACTIONS

The following adverse reactions are described in greater detail in other sections:

- Psychiatric Events Including Suicidality *[see Warnings and Precautions (5.2)]*
- Weight Decrease *[see Warnings and Precautions (5.3)]*

6.1 Adverse Reactions in Clinical Studies

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described below reflect exposure of 4438 patients to DALIRESP 500 mcg once daily in four 1-year placebo-controlled trials, two 6-month placebo-controlled trials, and two 6-month drug add-on trials *[see Clinical Studies (14.1)]*. In these trials, 3136 and 1232 COPD patients were exposed to DALIRESP 500 mcg once daily for 6 months and 1-year, respectively.

The population had a median age of 64 years (range 40-91), 73% were male, 92.9% were Caucasian, and had COPD with a mean pre-bronchodilator forced expiratory volume in one second (FEV_1) of 8.9 to 89.1% predicted. In these trials, 68.5% of the patients treated with DALIRESP reported an adverse reaction compared with 65.3% treated with placebo.

The proportion of patients who discontinued treatment due to adverse reaction was 14.8% for DALIRESP-treated patients and 9.9% for placebo-treated patients. The most common adverse reactions that led to discontinuation of DALIRESP were diarrhea (2.4%) and nausea (1.6%).

Serious adverse reactions, whether considered drug-related or not by the investigators, which occurred more frequently in DALIRESP-treated patients include diarrhea, atrial fibrillation, lung cancer, prostate cancer, acute pancreatitis, and acute renal failure.

Table 1 summarizes the adverse reactions reported by ≥ 2% of patients in the DALIRESP group in 8 controlled COPD clinical trials.

Table 1: Adverse Reactions Reported by ≥ 2% of Patients Treated with DALIRESP 500 mcg daily and Greater Than Placebo

	Treatment	
Adverse Reactions (Preferred Term)	**DALIRESP** (**N**=4438) n (%)	**Placebo** (**N**=4192) n (%)
Diarrhea	420 (9.5)	113 (2.7)
Weight decreased	331 (7.5)	89 (2.1)
Nausea	209 (4.7)	60 (1.4)
Headache	195 (4.4)	87 (2.1)
Back pain	142 (3.2)	92 (2.2)
Influenza	124 (2.8)	112 (2.7)
Insomnia	105 (2.4)	41 (1.0)
Dizziness	92 (2.1)	45 (1.1)
Decreased appetite	91 (2.1)	15 (0.4)

Adverse reactions that occurred in the DALIRESP group at a frequency of 1 to 2% where rates exceeded that in the placebo group include:

Gastrointestinal disorders - abdominal pain, dyspepsia, gastritis, vomiting
Infections and infestations - rhinitis, sinusitis, urinary tract infection,
Musculoskeletal and connective tissue disorders - muscle spasms
Nervous system disorders - tremor
Psychiatric disorders - anxiety, depression

7 DRUG INTERACTIONS

A major step in roflumilast metabolism is the N-oxidation of roflumilast to roflumilast N-oxide by CYP3A4 and CYP1A2 [*see Clinical Pharmacology (12.3)*].

7.1 Drugs That Induce Cytochrome P450 (CYP) Enzymes

Strong cytochrome P450 enzyme inducers decrease systemic exposure to roflumilast and may reduce the therapeutic effectiveness of DALIRESP. Therefore the use of strong cytochrome P450 inducers (e.g., rifampicin, phenobarbital, carbamazepine, and phenytoin) with DALIRESP is not recommended *[see Drug Interactions (5.4) and Clinical Pharmacology (12.3)]*.

7.2 Drugs That Inhibit Cytochrome P450 (CYP) Enzymes

The co-administration of DALIRESP (500 mcg) with CYP3A4 inhibitors or dual inhibitors that inhibit both CYP3A4 and CYP1A2 simultaneously (e.g., erythromycin, ketoconazole, fluvoxamine, enoxacin, cimetidine) may increase roflumilast systemic exposure and may result in increased adverse reactions. The risk of such concurrent use should be weighed carefully against benefit. *[see Clinical Pharmacology (12.3)]*.

7.3 Oral Contraceptives Containing Gestodene and Ethinyl Estradiol

The co-administration of DALIRESP (500 mcg) with oral contraceptives containing gestodene and ethinyl estradiol may increase roflumilast systemic exposure and may result in increased side effects. The risk of such concurrent use should be weighed carefully against benefit *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic effects: Pregnancy Category C: There are no adequate and well controlled studies of DALIRESP in pregnant women. DALIRESP was not teratogenic in mice, rats, or rabbits. DALIRESP should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

DALIRESP induced stillbirth and decreased pup viability in mice at doses corresponding to approximately 16 and 49 times, respectively, the maximum recommended human dose (MRHD) (on a mg/m^2 basis at maternal doses > 2 mg/kg/day and 6 mg/kg/day, respectively). DALIRESP induced post-implantation loss in rats at doses greater than or equal to approximately 10 times the MRHD (on a mg/m^2 basis at maternal doses ≥ 0.6 mg/kg/day). No treatment-related effects on embryo-fetal development were observed in

mice, rats, and rabbits at approximately 12, 3, and 26 times the MRHD, respectively (on a mg/m^2 basis at maternal doses of 1.5, 0.2, and 0.8 mg/kg/day, respectively).

Nonteratogenic effects: DALIRESP has been shown to adversely affect pup post-natal development when dams were treated with the drug during pregnancy and lactation periods in mice. These studies found that DALIRESP decreased pup rearing frequencies at approximately 49 times the MRHD (on a mg/mg^2 basis at a maternal dose of 6 mg/kg/day) during pregnancy and lactation. DALIRESP also decreased survival and forelimb grip reflex and delayed pinna detachment in mouse pups at approximately 97 times the MRHD (on a mg/m^2 basis at a maternal dose of 12 mg/kg/day) during pregnancy and lactation.

8.2 Labor and Delivery
DALIRESP should not be used during labor and delivery. There are no human studies that have investigated effects of DALIRESP on preterm labor or labor at term; however, animal studies showed that DALIRESP disrupted the labor and delivery process in mice. DALIRESP induced delivery retardation in pregnant mice at doses greater than or equal to approximately 16 times the MRHD (on a mg/m^2 basis at a maternal dose of > 2 mg/kg/day).

8.3 Nursing Mothers
Roflumilast and/or its metabolites are excreted into the milk of lactating rats. Excretion of roflumilast and/or its metabolites into human milk is probable. There are no human studies that have investigated effects of DALIRESP on breast-fed infants. DALIRESP should not be used by women who are nursing.

8.4 Pediatric Use
COPD does not normally occur in children. The safety and effectiveness of DALIRESP in pediatric patients have not been established.

8.5 Geriatric Use
Of the 4438 COPD subjects exposed to DALIRESP for up to 12 months in 8 controlled clinical trials, 2022 were > 65 years of age and 471 were > 75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Based on available data for roflumilast, no adjustment of dosage in geriatric patients is warranted *[see Clinical Pharmacology (12.3)]*.

8.6 Hepatic Impairment
Roflumilast 250 mcg once daily for 14 days was studied in subjects with mild-to-moderate hepatic impairment classified as Child-Pugh A and B (8 subjects in each group). The AUCs of roflumilast and roflumilast N-oxide were increased by 51% and 24%, respectively in Child-Pugh A subjects and by 92% and 41%, respectively in Child-Pugh B subjects, as compared to age-, weight- and gender-matched healthy subjects. The C_{max} of roflumilast and roflumilast N-oxide were increased by 3% and 26%, respectively in Child-Pugh A subjects and by 26% and 40%, respectively in Child-Pugh B subjects, as compared to healthy subjects. DALIRESP 500 mcg has not been studied in hepatically impaired patients. Clinicians should consider the risk-benefit of administering DALIRESP to patients who have mild liver impairment (Child-Pugh A). DALIRESP is not recommended for use in patients with moderate or severe liver impairment (Child-Pugh B or C) *[see Contraindications (4) and Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment
In twelve subjects with severe renal impairment administered a single dose of 500 mcg roflumilast, the AUCs of roflumilast and roflumilast N-oxide were decreased by 21% and 7%, respectively and C_{max} were reduced by 16% and 12%, respectively. No dosage adjustment is necessary for patients with renal impairment *[see Clinical Pharmacology (12.3)]*.

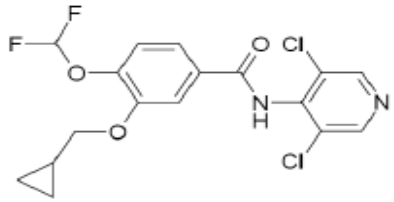
10 OVERDOSAGE

10.1 Human Experience
No case of overdose has been reported in clinical studies with DALIRESP. During the Phase I studies of DALIRESP, the following symptoms were observed at an increased rate after a single oral dose of 2500 mcg and a single dose of 5000 mcg: headache, gastrointestinal disorders, dizziness, palpitations, lightheadedness, clamminess and arterial hypotension.

10.2 Management of Overdose
In case of overdose, patients should seek immediate medical help. Appropriate supportive medical care should be provided. Since roflumilast is highly protein bound, hemodialysis is not likely to be an efficient method of drug removal. It is not known whether roflumilast is dialyzable by peritoneal dialysis.

11 DESCRIPTION
The active ingredient in DALIRESP tablets is roflumilast. Roflumilast and its active metabolite (roflumilast N-oxide) are selective phosphodiesterase 4 (PDE4) inhibitors. The chemical name of roflumilast is N-(3,5-dichloropyridin-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxy-benzamide. Its empirical formula is $C_{17}H_{14}Cl_2F_2N_2O_3$ and the molecular weight is 403.22.

The chemical structure is:



The drug substance is a white to off-white non-hygroscopic powder with a melting point of 160°C. It is practically insoluble in water and hexane, sparingly soluble in ethanol and freely soluble in acetone.

DALIRESP is supplied as white to off-white, round tablets, embossed with "D" on one side and "500" on the other side. Each tablet contains 500 mcg of roflumilast.

Each tablet of DALIRESP for oral administration contains the following inactive ingredients: lactose monohydrate, corn starch, povidone and magnesium stearate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Roflumilast and its active metabolite (roflumilast N-oxide) are selective inhibitors of phosphodiesterase 4 (PDE4). Roflumilast and roflumilast N-oxide inhibition of PDE4 (a major cyclic-3',5'-adenosine monophosphate (cyclic AMP)-metabolizing enzyme in lung tissue) activity leads to accumulation of intracellular cyclic AMP. While the specific mechanism(s) by which DALIRESP exerts its therapeutic action in COPD patients is not well defined, it is thought to be related to the effects of increased intracellular cyclic AMP in lung cells.

12.2 Pharmacodynamics

In COPD patients, 4 week treatment with DALIRESP 500 mcg oral once daily reduced sputum neutrophils and eosinophils by 31%, and 42%, respectively. In a pharmacodynamic study in healthy volunteers, DALIRESP 500 mcg once daily reduced the number of total cells, neutrophils and eosinophils found in bronchoalveolar lavage fluid following segmental pulmonary lipopolysaccharide (LPS) challenge by 35%, 38% and 73%, respectively. The clinical significance of these findings is unknown.

12.3 Pharmacokinetics

Absorption

The absolute bioavailability of roflumilast following a 500 mcg oral dose is approximately 80%. Maximum plasma concentrations (C_{max}) of roflumilast typically occur approximately one hour after dosing (ranging from 0.5 to 2 hours) in the fasted state while plateau-like maximum concentrations of the N-oxide metabolite are reached in approximately eight hours (ranging from 4 to 13 hours). Food has no affect on total drug absorption, but delays time to maximum concentration (T_{max}) of roflumilast by one hour and reduces C_{max} by approximately 40%, however, C_{max} and T_{max} of roflumilast N-oxide are unaffected. An *in vitro* study showed that roflumilast and roflumilast N-oxide did not inhibit P-gp transporter.

Distribution

Plasma protein binding of roflumilast and its N-oxide metabolite is approximately 99% and 97%, respectively. Volume of distribution for single dose 500 mcg roflumilast is about 2.9 L/kg. Studies in rats with radiolabeled roflumilast indicate low penetration across the blood-brain barrier.

Metabolism

Roflumilast is extensively metabolized via Phase I (cytochrome P450) and Phase II (conjugation) reactions. The N-oxide metabolite is the only major metabolite observed in the plasma of humans. Together, roflumilast and roflumilast N-oxide account for the majority (87.5%) of total dose administered in plasma. In urine, roflumilast was not detectable while roflumilast N-oxide was only a trace metabolite (less than 1%). Other conjugated metabolites such as roflumilast N-oxide glucuronide and 4-amino-3,5-dichloropyridine N-oxide were detected in urine.

While roflumilast is three times more potent than roflumilast N-oxide at inhibition of the PDE4 enzyme *in vitro*, the plasma AUC of roflumilast N-oxide on average is about 10-fold greater than the plasma AUC of roflumilast.

In vitro studies and clinical drug-drug interaction studies suggest that the biotransformation of roflumilast to its N-oxide metabolite is mediated by CYP 1A2 and 3A4. Based on further *in vitro* results in human liver microsomes, therapeutic plasma concentrations of roflumilast and roflumilast N-oxide do not inhibit CYP 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4/5, or 4A9/11. Therefore, there is a low probability of relevant interactions with substances metabolized by these P450 enzymes. In addition, *in vitro* studies demonstrated no induction of the CYP 1A2, 2A6, 2C9, 2C19, or 3A4/5 and only a weak induction of CYP 2B6 by roflumilast.

Elimination
The plasma clearance after short-term intravenous infusion of roflumilast is on average about 9.6 L/h. Following an oral dose, the median plasma effective half-life of roflumilast and its N-oxide metabolite are approximately 17 and 30 hours, respectively. Steady state plasma concentrations of roflumilast and its N-oxide metabolite are reached after approximately 4 days for roflumilast and 6 days for roflumilast N-oxide following once daily dosing. Following intravenous or oral administration of radiolabeled roflumilast, about 70% of the radioactivity was recovered in the urine.

Special Populations

Hepatic Impairment
Roflumilast 250 mcg once daily for 14 days was studied in subjects with mild-to-moderate hepatic impairment classified as Child-Pugh A and B (8 subjects in each group). The AUC of roflumilast and roflumilast N-oxide were increased by 51% and 24%, respectively in Child-Pugh A subjects and by 92% and 41%, respectively in Child-Pugh B subjects, as compared to age-, weight- and gender-matched healthy subjects. The C_{max} of roflumilast and roflumilast N-oxide were increased by 3% and 26%, respectively in Child-Pugh A subjects and by 26% and 40%, respectively in Child-Pugh B subjects, as compared to healthy subjects. DALIRESP 500 mcg has not been studied in hepatically impaired patients. Clinicians should consider the risk-benefit of administering DALIRESP to patients who have mild liver impairment (Child-Pugh A). DALIRESP is not recommended for use in patients with moderate or severe liver impairment (Child-Pugh B or C) *[see Contraindications (4) and Use in Specific Populations (8.6)]*.

Renal Impairment
In twelve subjects with severe renal impairment administered a single dose of 500 mcg roflumilast, roflumilast and roflumilast N-oxide AUCs were decreased by 21% and 7%, respectively and C_{max} were reduced by 16% and 12%, respectively. No dosage adjustment is necessary for patients with renal impairment *[see Use in Specific Populations (8.7)]*.

Age
Roflumilast 500 mcg once daily for 15 days was studied in young, middle aged, and elderly healthy subjects. The exposure in elderly (> 65 years of age) were 27% higher in AUC and 16% higher in C_{max} for roflumilast and 19% higher in AUC and 13% higher in C_{max} for roflumilast-N-oxide than that in young volunteers (18-45 years old). No dosage adjustment is necessary for elderly patients *[see Use in Specific Populations (8.5)]*.

Gender
In a Phase I study evaluating the effect of age and gender on the pharmacokinetics of roflumilast and roflumilast N-oxide, a 39% and 33% increase in roflumilast and roflumilast N-oxide AUC were noted in healthy female subjects as compared to healthy male subjects. No dosage adjustment is necessary based on gender.

Smoking
The pharmacokinetics of roflumilast and roflumilast N-oxide were comparable in smokers as compared to non-smokers. There was no difference in C_{max} between smokers and non-smokers when roflumilast 500 mcg was administered as a single dose to 12 smokers and 12 non-smokers. The AUC of roflumilast in smokers was 13% less than that in non-smokers while the AUC of roflumilast N-oxide in smokers was 17% more than that in non-smokers.

Race
As compared to Caucasians, African Americans, Hispanics, and Japanese showed 16%, 41%, and 15% higher AUC, respectively, for roflumilast and 43%, 27%, and 16% higher AUC, respectively, for roflumilast N-oxide. As compared to Caucasians, African Americans, Hispanics, and Japanese showed 8%, 21%, and 5% higher C_{max}, respectively, for roflumilast and 43%, 27%, and 17% higher C_{max}, respectively, for roflumilast N-oxide. No dosage adjustment is necessary for race.

Drug Interactions
Drug interaction studies were performed with roflumilast and other drugs likely to be coadministered or drugs commonly used as probes for pharmacokinetic interaction [*see Drug Interactions*]. No significant drug interactions were observed when 500 mcg oral roflumilast was administered with inhaled salbutamol, formoterol, budesonide and oral montelukast, digoxin, theophylline, warfarin, sildenafil, midazolam, or antacids.

The effect of concomitant drugs on the exposure of roflumilast and roflumilast N-oxide is shown in the Figure 1 below.

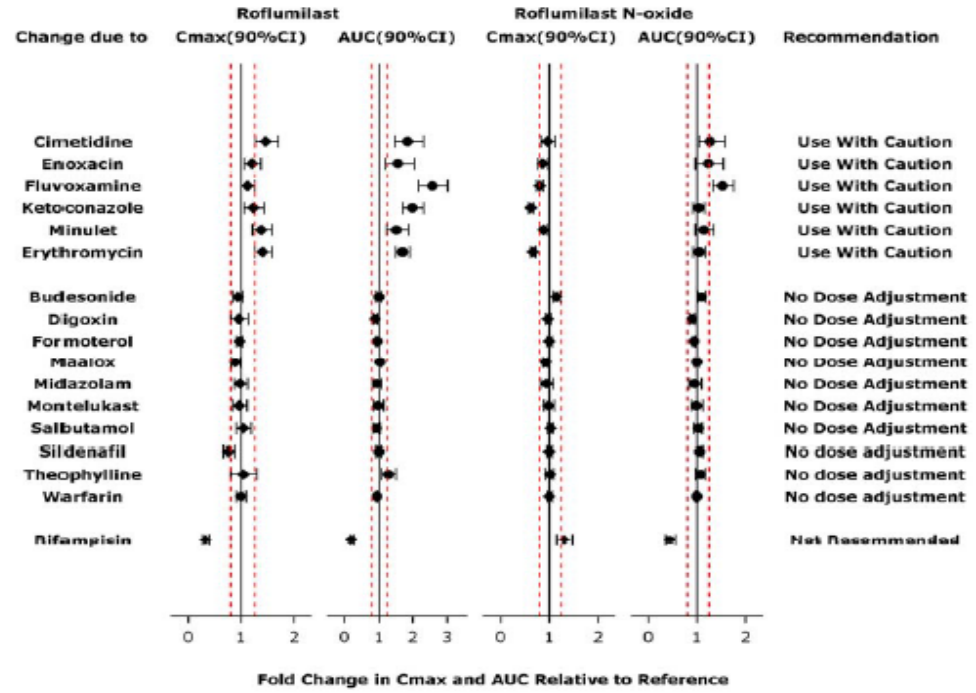


Figure 1. Effect of concomitant drugs on the exposure of roflumilast and roflumilast N-oxide. Note that the dashed lines indicate the lower and higher bounds (0.8-1.25) of the 90% confidence interval of the geometric mean ratio of Cmax or AUC for roflumilast or roflumilast N-oxide for Treatment (DALIRESP+Coadministered Drug) vs. Reference (DALIRESP). The dosing regimens of coadministered drugs was: Midazolam:2mg po SD; Erythromycin:500mg po TID; Ketoconazole:200mg po BID; Rifampicin:600mg po QD; Fluvoxamine:50mg po QD; Digoxin:250ug po SD; Maalox:30mL po SD; Salbutamol:0.2mg pi TID; Cimetidine:400mg po BID; Formoterol:40ug po BID; Budesonide:400ug po BID; Theophylline:375mg po BID; Warfarin:250mg po SD; Enoxacin:400mg po BID; Sildenafil:100mg SD; Minulet (combination oral contraceptive):0.075mg gestodene/0.03mg ethinylestradiol po QD; Montelukast:10mg po QD

Drug interactions considered to be significant are described in more detail below *[also see Drug Interactions (5.4) and Drug Interactions (7)]*.

Inhibitors of CYP3A4 and CYP1A2:
Erythromycin: In an open-label crossover study in 16 healthy volunteers, the coadministration of CYP 3A4 inhibitor erythromycin (500 mg three times daily for 13 days) with a single oral dose of 500 mcg DALIRESP resulted in 40% and 70% increase in C_{max} and AUC for roflumilast, respectively, and a 34% decrease and a 4% increase in C_{max} and AUC for roflumilast N-oxide, respectively.

Ketoconazole: In an open-label crossover study in 16 healthy volunteers, the coadministration of a strong CYP 3A4 inhibitor ketoconazole (200 mg twice daily for 13 days) with a single oral dose of 500 mcg DALIRESP resulted in 23% and 99% increase in C_{max} and AUC for roflumilast, respectively, and a 38% reduction and 3% increase in C_{max} and AUC for roflumilast N-oxide, respectively.

Fluvoxamine: In an open-label crossover study in 16 healthy volunteers, the coadministration of dual CYP 3A4/1A2 inhibitor fluvoxamine (50 mg daily for 14 days) with a single oral dose of 500 mcg DALIRESP showed a 12% and 156% increase in roflumilast C_{max} and AUC along with a 210% decrease and 52% increase in roflumilast N-oxide C_{max} and AUC, respectively.

Enoxacin: In an open-label crossover study in 16 healthy volunteers, the coadministration of dual CYP 3A4/1A2 inhibitor enoxacin (400 mg twice daily for 12 days) with a single oral dose of 500 mcg DALIRESP resulted in an increased C_{max} and AUC of roflumilast by 20% and 56%, respectively. Roflumilast N-oxide C_{max} was decreased by 14% while roflumilast N-oxide AUC was increased by 23%.

Cimetidine: In an open-label crossover study in 16 healthy volunteers, the coadministration of a dual CYP 3A4/1A2 inhibitor cimetidine (400 mg twice daily for 7 days) with a single dose of 500 mcg oral DALIRESP resulted in a 46% and 85% increase in roflumilast C_{max} and AUC; and a 4% decrease in C_{max} and 27% increase in AUC for roflumilast N-oxide, respectively.
Oral Contraceptives containing Gestodene and Ethinyl Estradiol:
In an open-label crossover study in 20 healthy adult volunteers, coadministration of a single oral dose of 500 mcg DALIRESP with repeated doses of a fixed combination oral contraceptive containing 0.075 mg gestodene and 0.03 mg ethinyl estradiol to steady state caused a 38% increase and 12 % decrease in C_{max} of roflumilast and roflumilast N-oxide, respectively. Roflumilast and roflumilast N-oxide AUCs were increased by 51% and 14%, respectively.

Inducers of CYP enzymes:
Rifampicin: In an open-label, three-period, fixed-sequence study in 15 healthy volunteers, coadministration of the strong CYP3A4 inducer rifampicin (600 mg once daily for 11 days) with a single oral dose of 500 mcg DALIRESP resulted in reduction of roflumilast C_{max} and AUC by 68% and 79%, respectively; and an increase of roflumilast N-oxide C_{max} by 30% and reduced roflumilast N-oxide AUC by 56%.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies were conducted in hamsters and mice with roflumilast to evaluate its carcinogenic potential. In 2-year oral gavage carcinogenicity studies, roflumilast treatment resulted in dose-related, statistically significant increases in the incidence of undifferentiated carcinomas of nasal epithelium in hamsters at ≥ 8 mg/kg/day (approximately 11 times the MRHD based on summed AUCs of roflumilast and its metabolites). The tumorigenicity of roflumilast appears to be attributed to a reactive metabolite of 4-amino-3,5-dichloro-pyridine N-oxide (ADCP N-oxide). No evidence of tumorigenicity was observed in mice at roflumilast oral doses up to 12 and 18 mg/kg/day in females and males, respectively (approximately 10 and 15 times the MRHD, respectively, based on summed AUCs of roflumilast and its metabolites).

Roflumilast tested positive in an *in vivo* mouse micronucleus test, but negative in the following assays: Ames test for bacterial gene mutation, *in vitro* chromosome aberration assay in human lymphocytes, *in vitro* HPRT test with V79 cells, an *in vitro* micronucleus test with V79 cells, DNA adduct formation assay in rat nasal mucosa, liver and testes, and *in vivo* mouse bone marrow chromosome aberration assay. Roflumilast N-oxide was negative in the Ames test and in vitro micronucleus test with V79 cells.

In a human spermatogenesis study, roflumilast 500 mcg had no effects on semen parameters or reproductive hormones during the 3-month treatment period and the following 3-month off-treatment period. In a fertility study, roflumilast decreased fertility rates in male rats at 1.8-mg/kg/day (approximately 29 times the MRHD on a mg/m^2 basis). These rats also showed increases in the incidence of tubular atrophy, degeneration in the testis and spermiogenic granuloma in the epididymides. No effect on male rat fertility rate or reproductive organ morphology was observed at 0.8 mg/kg/day (approximately 13 times the MRHD on a mg/m^2 basis). No effect on female fertility was observed up to the highest roflumilast dose of 1.5 mg/kg/day in rats (approximately 24 times the MRHD on a mg/m^2 basis).

14 CLINICAL STUDIES

14.1 Chronic Obstructive Pulmonary Disease (COPD)

The efficacy and safety of DALIRESP (roflumilast) in COPD was evaluated in 8 randomized double-blind, controlled, parallel group clinical trials in 9394 adult patients (4425 receiving DALIRESP 500 mcg) 40 years of age and older with COPD. Of the 8 trials, two were placebo-controlled dose selection trials (Trials 1 and 2) of 6 months duration that evaluated the efficacy of DALIRESP 250 mcg and 500 mcg once daily, four were placebo-controlled 1-year trials (Trials 3, 4, 5, and 6) primarily designed to evaluate the efficacy of DALIRESP on COPD exacerbations, and two were 6-month efficacy trials (Trials 7 and 8) which assessed the effect of DALIRESP as add-on therapy to a long-acting beta agonist or long-acting anti-muscarinic. The 8 trials enrolled patients with nonreversible obstructive lung disease (FEV_1/FVC ≤ 70% and ≤ 12% or 200 mL improvement in FEV_1 in response to 4 puffs of albuterol/salbutamol) but the severity of airflow obstruction at baseline was different among the trials. Patients enrolled in the dose selection trials had the full range of COPD severity (FEV_1 30-80% predicted); median age of 63 years, 73% male, and 99% Caucasian. Patients enrolled in the four exacerbation trials had severe COPD (FEV_1 ≤ 50% predicted); median age of 64 years, 74% male, and 90% Caucasian. Patients enrolled in the two 6-month efficacy trials had moderate to severe COPD (FEV_1 40-70% predicted); median age of 65 years, 68% male, and 97% Caucasian. COPD exacerbations and lung function (FEV_1) were co-primary efficacy outcome measures in the four 1-year trials. In the two 6-month supportive efficacy trials, lung function (FEV_1) alone was the primary efficacy outcome measure.

The two 6-month dose-selection efficacy trials (Trials 1 and 2) explored doses of 250 mcg and 500 mcg once daily in a total of 1929 patients (751 and 724 on DALIRESP 250 and 500 mcg, respectively). The selection of the 500 mcg dose was primarily based on nominal improvements in lung function (FEV_1) over the 250 mcg dose. The once daily dosing regimen was primarily based on the determination of a plasma half-life of 17 hours for roflumilast and 30 hours for its active metabolite roflumilast N-oxide [*see Clinical Pharmacology (12.3)*].

Effect on Exacerbations
The effect of DALIRESP 500 mcg once daily on COPD exacerbations was evaluated in four 1-year trials (Trials 3, 4, 5, and 6).

Two of the trials (Trials 3 and 4) conducted initially enrolled a population of patients with severe COPD (FEV_1 ≤ 50% of predicted) inclusive of those with chronic bronchitis and/or emphysema who had a history of smoking of at least 10 pack years. Inhaled

corticosteroids were allowed as concomitant medications and used in 61% of both DALIRESP and placebo-treated patients and short-acting beta agonists were allowed as rescue therapy. The use of long-acting beta agonists, long-acting anti-muscarinics, and theophylline were prohibited. The rate of moderate or severe COPD exacerbations was a co-primary endpoint in both trials. There was not a symptomatic definition of exacerbation in these 2 trials. Exacerbations were defined in terms of severity requiring treatment with a moderate exacerbation defined as treatment with systemic glucocorticosteroids in Trial 3 or systemic glucocorticosteroids and/or antibiotics in Trial 4 and a severe exacerbation defined as requiring hospitalizations and/or leading to death in Trial 3 or requiring hospitalization in Trial 4. The trials randomized 1176 patients (567 on DALIRESP) in Trial 3 and 1514 patients (760 on DALIRESP) in Trial 4. Both trials failed to demonstrate a significant reduction in the rate of COPD exacerbations.

Exploratory analyses of the results of Trials 3 and 4 identified a subpopulation of patients with severe COPD associated with chronic bronchitis and COPD exacerbations within the previous year that appeared to demonstrate a better response in the reduction of the rate of COPD exacerbations compared to the overall population. As a result, two subsequent trials (Trial 5 and Trial 6) were conducted that enrolled patients with severe COPD but associated with chronic bronchitis, at least one COPD exacerbation in the previous year, and at least a 20 pack-year smoking history. In these trials, long-acting beta agonists and short-acting anti-muscarinics were allowed and were used by 44% and 35% of patients treated with DALIRESP and 45% and 37% of patients treated with placebo, respectively. The use of inhaled corticosteroids was prohibited. As in trials 3 and 4, the rate of moderate exacerbations (defined as requiring intervention with systemic glucocorticosteroids) or severe exacerbations (defined as leading to hospitalization and/or to death) was a co-primary endpoint.

Trial 5 randomized a total of 1525 patients (765 on DALIRESP) and Trial 6 randomized a total of 1571 patients (772 on DALIRESP). In both trials, DALIRESP 500 mcg once daily demonstrated a significant reduction in the rate of moderate or severe exacerbations compared to placebo (Table 2). These two trials provide the evidence to support the use of DALIRESP for the reduction of COPD exacerbations.

Table 2. Effect of DALIRESP on Rate of Moderate or Severe Exacerbations

Study	Exacerbations Per Patient-Year					
	DALIRESP	Placebo	Absolute Reduction[1]	RR[2]	95% CI	Percent Reduction[3]
Trial 5	1.1	1.3	0.2	0.85	0.74, 0.98	15
Trial 6	1.2	1.5	0.3	0.82	0.71, 0.94	18

1. Absolute reduction measured as difference between placebo and roflumilast treated patients.
2. RR is Rate Ratio.
3. Percent reduction is defined as 100 (1-RR).

For patients in Trials 5 and 6 who received concomitant long-acting beta agonists or short-acting anti-muscarinics, reduction of moderate or severe exacerbations with DALIRESP was similar to that observed for the overall populations of the two trials.

Effect on Lung Function
While DALIRESP is not a bronchodilator, all 1-year trials (Trials 3, 4, 5, and 6) evaluated the effect of DALIRESP on lung function as determined by the difference in FEV_1 between DALIRESP and placebo-treated patients (pre-bronchodilator FEV_1 measured prior to study drug administration in three of the trials and post-bronchodilator FEV_1 measured 30 minutes after administration of 4 puffs of albuterol/salbutamol in one trial) as a co-primary endpoint. In each of these trials DALIRESP 500 mcg once daily demonstrated a statistically significant improvement in FEV_1 which averaged approximately 50 mL across the four trials. Table 3 shows FEV_1 results from Trials 5 and 6 which had demonstrated a significant reduction in COPD exacerbations.

Table 3. Effect of DALIRESP on FEV_1

Study	Change in FEV_1 from Baseline, mL			
	DALIRESP	Placebo	Effect[1]	95% CI
Trial 5	46	8	39	18, 60
Trial 6	33	-25	58	41, 75

[1] Effect measured as difference between DALIRESP and placebo treated patients.

Lung function was also evaluated in two 6-month trials (Trials 7 and 8) to assess the effect of DALIRESP when administered as add-on therapy to treatment with a long-acting beta agonist or a long-acting anti-muscarinic. These trials were conducted in a different population of COPD patients [moderate to severe COPD (FEV_1 40 to 70% of predicted) without a requirement for chronic bronchitis or frequent history of exacerbations] from that for which efficacy in reduction of exacerbations has been demonstrated and provide safety support to the DALIRESP COPD program.

No trials have been conducted to assess the effects of DALIRESP on COPD exacerbations when added to a fixed-dose combination product containing a long-acting beta agonist and inhaled corticosteroid.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

DALIRESP is supplied as white to off-white, round tablets, embossed with "D" on one side and "500" on the other side. Each tablet contains 500 mcg of roflumilast.

DALIRESP tablets are available:

Bottles of 30:	NDC 0456-0095-30
Bottles of 90:	NDC 0456-0095-90
10X10 Unit Dose:	NDC 0456-0095-63

16.2 Storage and Handling

Store DALIRESP 500 mcg tablets at 20° - 25°C (68° - 77°F); excursions permitted to 15° - 30°C (59° - 86°F). [See USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-approved Medication Guide.

17.1 Bronchospasm

DALIRESP is not a bronchodilator and should not be used for the relief of acute bronchospasm. *[see Warnings and Precautions (5.1)]*.

17.2 Psychiatric Events including Suicidality

Treatment with DALIRESP is associated with an increase in psychiatric adverse reactions. In clinical trials, 5.9% (263) of patients treated with DALIRESP 500 mcg daily reported psychiatric adverse reactions compared to 3.3% (137) treated with placebo. The most commonly reported psychiatric adverse events were insomnia, anxiety, and depression which were reported at higher rates in those treated with DALIRESP 500 mcg (2.4%, 1.4%, and 1.2% for DALIRESP versus 1.0%, 0.9%, and 0.9% for placebo, respectively). Instances of suicidal ideation and behavior, including completed suicide, have been observed in clinical trials. Three patients experienced suicide-related adverse reactions (one completed suicide and two suicide attempts) while receiving DALIRESP compared to one patient (suicidal ideation) who received placebo.

Before using DALIRESP in patients with a history of depression and/or suicidal thoughts or behavior, prescribers should carefully weigh the risks and benefits of treatment with DALIRESP in such patients. Patients, their caregivers, and families should be advised of the need to be alert for the emergence or worsening of insomnia, anxiety, depression, suicidal thoughts or other mood changes, and if such changes occur to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment with DALIRESP if such events occur *[see Warnings and Precautions (5.2)]*.

17.3 Weight Decrease

Weight loss was a common adverse reaction in DALIRESP clinical trials and was reported in 7.5% (331) of patients treated with DALIRESP 500 mcg once daily compared to 2.1% (89) treated with placebo. In two placebo-controlled clinical trials of one year duration in which weight was prospectively assessed, 20% of patients receiving roflumilast experienced moderate weight loss (defined as between 5-10% of body weight) compared to 7% of patients who received placebo and 7% of patients who received roflumilast compared to 2% of patients receiving placebo experienced severe (>10% body weight) weight loss. During follow-up after treatment discontinuation, the majority of patients with weight loss regained some of the weight they had lost while receiving DALIRESP. Patients treated with DALIRESP should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated, and discontinuation of DALIRESP should be considered *[see Warnings and Precautions (5.3)]*.

17.4 Drug Interactions

The administration of the cytochrome P450 enzyme inducer rifampicin resulted in a reduction in exposure which may result in a decrease in the therapeutic effectiveness of DALIRESP. Therefore, the use of strong cytochrome P450 enzyme inducers (e.g. rifampicin, phenobarbital, carbamazepine, phenytoin) with DALIRESP is not recommended [*see Drugs That Induce Cytochrome P450 (CYP) Enzymes (7.1) and Clinical Pharmacology (12.3)*].

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MEDICATION GUIDE
DALIRESP® (da'-li-resp)
(roflumilast)
Tablets

Read this Medication Guide before you start taking DALIRESP® and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment.

What is the most important information I should know about DALIRESP?

DALIRESP can cause serious side effects. Tell your healthcare provider right away if you have any of the symptoms listed below while taking DALIRESP.

1. **DALIRESP may cause mental health problems including suicidal thoughts and behavior.** Some people taking DALIRESP may develop mood or behavior problems including:

   - thoughts of suicide or dying
   - attempt to commit suicide
   - trouble sleeping (insomnia)
   - new or worse anxiety
   - new or worse depression
   - acting on dangerous impulses
   - other unusual changes in your behavior or mood

2. **Weight loss.** DALIRESP can cause weight loss. You should check your weight on a regular basis. You will also need to see your healthcare provider regularly to have your weight checked. If you notice that you are losing weight, call your healthcare provider. Your healthcare provider may ask you to stop taking DALIRESP if you lose too much weight.

DALIRESP may affect the way other medicines work, and other medicines may affect how DALIRESP works. Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

What is DALIRESP?

DALIRESP is a prescription medicine used in adults with severe Chronic Obstructive Pulmonary Disease (COPD) to decrease the number of flare-ups or the worsening of COPD symptoms (exacerbations).

DALIRESP is not a bronchodilator and should not be used for treating sudden breathing problems. Your healthcare provider may give you other medicine to use for sudden breathing problems.

It is not known if DALIRESP is safe and effective in children.

Who should not take DALIRESP?

Do not take DALIRESP if you:

- have certain liver problems. Talk with your healthcare provider before you take DALIRESP if you have liver problems.

What should I tell my healthcare provider before taking DALIRESP?

Before you take DALIRESP, tell your healthcare provider if you:

- have or have had a history of mental health problems including depression and suicidal behavior.
- have liver problems
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if DALIRESP will harm your unborn baby. Talk to your healthcare provider if you are pregnant or plan to become pregnant.

- are breastfeeding or plan to breastfeed. It is not known if DALIRESP passes into your breast milk. You and your healthcare provider should decide if you will take DALIRESP or breastfeed. You should not do both.

How should I take DALIRESP?

- Take DALIRESP exactly as your healthcare provider tells you to take it.
- DALIRESP can be taken with or without food.
- If you take more than your prescribed dose of DALIRESP, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of DALIRESP?

DALIRESP can cause serious side effects, including:

See "**What is the most important information I should know about DALIRESP?**"

The most common side effects of DALIRESP include:

- diarrhea
- weight loss
- nausea
- headache
- back pain
- flu like symptoms
- problems sleeping (insomnia)
- dizziness
- decreased appetite

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of DALIRESP.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store DALIRESP Tablets?

- **Store DALIRESP at 68°F to 77°F (20°C to 25°C); excursions permitted to 15° - 30°C (59° - 86°F). [See USP Controlled Room Temperature].**

Keep DALIRESP Tablets and all medicines out of the reach of children.

General information about DALIRESP

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use DALIRESP for a condition for which it was not prescribed. Do not give DALIRESP to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about DALIRESP. For more information about DALIRESP, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about DALIRESP that is written for health professionals.

For more information about DALIRESP call 1-800-678-1605.

What are the ingredients in DALIRESP?

Active ingredient: roflumilast
Inactive ingredients: lactose monohydrate, corn starch, povidone and magnesium stearate.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Rev. 02/2011

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Appendix 4: Quality of Life Enjoyment and Satisfaction Questionnaire

PJS 5-16-2007

Quality of Life Enjoyment and Satisfaction Questionnaire
Q-Les-Q

Jean Endicott, Ph.D.*

This questionnaire is designed to help assess the degree of enjoyment and satisfaction experienced during the past week.

Name_____ ID #_____ Date_____
(3-10)+ (11-16)+

Sex: 1 - Male, 2 - Female Age:_____
(17)+ (18-19)+

Study #_____ Group_____
(20-21)+ (22-24)+

(79-80 = DA+)
6/13/95-R

* Developed with the assistance of Wilma Harrison, M.D. and Dianne Schechter, Ph.D. (11/29/90)
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+ Keypunch: Duplicate on all cards.

PHYSICAL HEALTH/ACTIVITIES

With regard to your physical health, during the past week how much of the time have you ...	Not at all or never	Rarely	Some-times	Often or most of the time	Frequently or all the time	
... been completely free of aches, pains, or discomfort?	1	2	3	4	5	(25)
... felt rested?	1	2	3	4	5	(26)
... felt energetic?	1	2	3	4	5	(27)
... felt in excellent physical health?	1	2	3	4	5	(28)
... felt in at least very good physical health?	1	2	3	4	5	(29)
... been free of worry about your physical health?	1	2	3	4	5	(30)
... felt you got enough sleep?	1	2	3	4	5	(31)
... felt able to be as physically active as needed?	1	2	3	4	5	(32)
... felt well coordinated?	1	2	3	4	5	(33)
... felt your memory was functioning well?	1	2	3	4	5	(34)
... felt good physically?	1	2	3	4	5	(35)
... felt full of pep and vitality?	1	2	3	4	5	(36)
... been free of visual problems?	1	2	3	4	5	(37)

FEELINGS

During the past week, how much of the time have you....	Not at all or never	Rarely	Some-times	Often or most of the time	Frequently or all the time	
... felt clearheaded?	1	2	3	4	5	(38)
... felt satisfied with your life?	1	2	3	4	5	(39)
... felt good about your appearance?	1	2	3	4	5	(40)
... felt happy or cheerful?	1	2	3	4	5	(41)
... felt independent?	1	2	3	4	5	(42)
... felt content?	1	2	3	4	5	(43)
... felt able to communicate with others?	1	2	3	4	5	(44)
... felt interested in taking care of your appearance (hair, clothing) and personal hygiene (bathing, dressing)?	1	2	3	4	5	(45)
... felt able to make decisions?	1	2	3	4	5	(46)
... felt relaxed?	1	2	3	4	5	(47)
... felt good about your life?	1	2	3	4	5	(48)
... felt able to travel about to get things done when needed (walk, use car, bus, train, or whatever is available as needed)?	1	2	3	4	5	(49)
... felt able to deal with life's problems?	1	2	3	4	5	(50)
... felt able to take care of yourself?	1	2	3	4	5	(51)

WORK

Do you:
have a job_____?
work for yourself_____?
do volunteer work_____?

IF:
1 - NO to all 3 (Note reason & SKIP to Page 4)

2 - YES to any of the 3 (COMPLETE THIS SECTION) (52)

1. Too ill physically
2. Too emotionally upset
3. Retired
4. Other_____ (71)
_____
(write in reason)

During the past week, how often have you....	Not at all or never	Rarely	Some-times	Often or most of the time	Frequently or all the time	
... enjoyed your work?	1	2	3	4	5	(57)
... solved work problems or dealt with them without undue stress?	1	2	3	4	5	(58)
... thought clearly about work?	1	2	3	4	5	(59)
... been decisive about work, or made decisions when needed?	1	2	3	4	5	(60)
... accomplished what you wanted to do?	1	2	3	4	5	(61)
... been pleased with your work accomplishments?	1	2	3	4	5	(62)
... worked well?	1	2	3	4	5	(63)
... been interested in your work?	1	2	3	4	5	(64)
... concentrated on work?	1	2	3	4	5	(65)
... worked carefully?	1	2	3	4	5	(66)
... kept up with expected work?	1	2	3	4	5	(67)
... taken care of work by yourself when it was necessary?	1	2	3	4	5	(68)
... communicated and interacted with ease with others while working?	1	2	3	4	5	(69)

HOUSEHOLD DUTIES

Are you responsible for any household duties/housework/homemaker activities (e.g., cleaning, shopping, doing dishes, food shopping or preparation) for yourself or for other people?

IF:
1 - NO to all 3 (Note reason and SKIP to Page 5)
2 - YES (COMPLETE THIS SECTION) (70)

1. Too ill physically
2. Too emotionally upset
3. Not expected to do anything
4. Other_____ (71)

_____
(write in reason)

During the past week, how often have you....	Not at all or never	Rarely	Some-times	Often or most of the time	Frequently or all the time	
... kept your room/apartment/house cleaned to your satisfaction?	1	2	3	4	5	(72)
... paid the bills, done the banking to your satisfaction?	1	2	3	4	5	(73)
... shopped for food or other household items to your satisfaction?	1	2	3	4	5	(74)
... prepared food or obtained food to your satisfaction?	1	2	3	4	5	(75)
... taken care of the laundry/cleaning to your satisfaction?	1	2	3	4	5	(76)
... had a feeling of accomplishment with regard to household activities?	1	2	3	4	5	(225)
... concentrated and thought clearly about what household activities need to be done?	1	2	3	4	5	(226)
... solved household problems or dealt with them without undue stress?	1	2	3	4	5	(227)
... been decisive or made decisions when needed with regard to household activities?	1	2	3	4	5	(228)
... made repairs or taken care of household maintenance as needed?	1	2	3	4	5	(229)

SCHOOL/COURSE WORK

Have you been taking any courses, going to class, or been involved in any type of course work, school or college studies during the past week?

IF:
1 - NO (Note reason and SKIP to Page 6)

2 - YES (COMPLETE THIS SECTION) (230)

1. Too ill physically
2. Too emotionally upset
3. Not expected to do anything
4. Other_____ (231)

_____ (write in reason)

During the past week, how much of the time have you....	Not at all or never	Rarely	Some-times	Often or most of the time	Frequently or all the time	
... enjoyed the course/class work?	1	2	3	4	5	(232)
... looked forward to getting to work on the course/class work?	1	2	3	4	5	(233)
... dealt with the course/class work without undue stress?	1	2	3	4	5	(234)
... thought clearly about the course/class work?	1	2	3	4	5	(235)
... been decisive about the course/class work when needed?	1	2	3	4	5	(236)
... been pleased with your course/class work accomplishments?	1	2	3	4	5	(237)
... been interested in your course/class work?	1	2	3	4	5	(238)
... concentrated on the course/class work?	1	2	3	4	5	(239)
... felt good while doing your course/class work?	1	2	3	4	5	(240)
... communicated and interacted with ease with others at your course/class work?	1	2	3	4	5	(241)

LEISURE TIME ACTIVITIES

The following questions refer to leisure time activities such as watching TV, reading the paper or magazines, tending house plants or gardening, hobbies, going to museums or the movies, or to sports events, etc.

	Not at all or never	Rarely	Some-times	Often or most of the time	Frequently or all the time	
When you had time, how often did you use that time for a leisure time activity?	1	2	3	4	5	(244)
How often did you enjoy the leisure activities?	1	2	3	4	5	(245)
How often did you look forward to the leisure activities before spending time at them?	1	2	3	4	5	(246)
How often did you concentrate on the leisure activities and pay attention to them?	1	2	3	4	5	(247)
If a problem arose in your leisure activities, how often did you solve it or deal with it without undue stress?	1	2	3	4	5	(248)
How often did the leisure activities sustain your interest?	1	2	3	4	5	(249)

SOCIAL RELATIONS

	Not at all or never	Rarely	Some-times	Often or most of the time	Frequently or all the time	
During the past week, how often have you ...						
... enjoyed talking with or being with friends or relatives?	1	2	3	4	5	(250)
... looked forward to getting together with friends or relatives?	1	2	3	4	5	(251)
... made social plans with friends or relatives for future activities?	1	2	3	4	5	(252)
... enjoyed talking with co-workers or neighbors?	1	2	3	4	5	(253)
... been patient with others when others were irritating in their actions or words?	1	2	3	4	5	(254)
... been interested in the problems of other people?	1	2	3	4	5	(255)
... felt affection toward one or more people?	1	2	3	4	5	(256)
... gotten along well with other people?	1	2	3	4	5	(257)
... joked or laughed with other people?	1	2	3	4	5	(258)
... felt you met the needs of friends or relatives?	1	2	3	4	5	(259)
... felt your relationships with your friends or relatives were without major problems or conflicts?	1	2	3	4	5	(260)

GENERAL ACTIVITIES

Taking everything into consideration, during the past week, how satisfied have you been with your...	OVERALL LEVEL OF SATISFACTION					
	Very Poor	Poor	Fair	Good	Very Good	
... physical health?	1	2	3	4	5	(261)
... mood?	1	2	3	4	5	(262)
... work?	1	2	3	4	5	(263)
... household activities?	1	2	3	4	5	(264)
... social relationships?	1	2	3	4	5	(265)
... family relationships?	1	2	3	4	5	(266)
... leisure time activities?	1	2	3	4	5	(267)
... ability to function in daily life?	1	2	3	4	5	(268)
... sexual drive, interest and/or performance?*	1	2	3	4	5	(269)
... economic status?	1	2	3	4	5	(270)
... living/housing situation?*	1	2	3	4	5	(271)
... ability to get around physically without feeling dizzy or unsteady or falling?*	1	2	3	4	5	(272)
... your vision in terms of ability to do work or hobbies?*	1	2	3	4	5	(273)
... overall sense of well being?	1	2	3	4	5	(274)
... medication? (If not taking any, check here _____ (275) and leave item blank)	1	2	3	4	5	(276)
How would you rate your overall life satisfaction and contentment during the past week?	1	2	3	4	5	(277)

* If satisfaction is very poor, poor or fair on these items, please UNDERLINE the factor(s) associated with a lack of satisfaction.