Clinical Trial Protocol: THR-1442-C-418

Study Title:	Efficacy and safety of EGT0001442 compared with placebo in patients with type 2 diabetes mellitus inadequately controlled by diet and exercise and up to one oral anti-diabetes agent.
Study Number:	THR-1442-C-418
Study Phase:	3
Product Name:	EGT0001442 tablet
IND Number:	103822
Indication:	Type 2 diabetes mellitus
Investigators:	Multiple center
Sponsor:	Theracos, Inc.
Sponsor Contact:	Albert Collinson, Ph.D. Theracos, inc. 550 Del Rey Avenue Sunnyvale, CA 94085 Phone: 408-992-1100
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	Date
Original Protocol:	02 February 2011

SYNOPSIS

Sponsor:

Theracos, Inc.

Name of Finished Product:
EGT0001442 tablet

Name of Active Ingredient:

EGT0001442

Study Title:
Efficacy and safety of EGT0001442 compared with placebo in patients with type 2 diabetes mellitus inadequately controlled by diet and exercise and up to one oral anti-diabetes agent.

Study Number:
THR-1442-C-418

Study Phase: 3

Primary Objective(s):
To assess the efficacy of EGT0001442 in lowering HbA1c at week 24 compared with placebo

Secondary Objective(s):

- To assess the efficacy of EGT0001442 in lowering FPG at weeks 2 and 24 compared with placebo
- To assess the efficacy of EGT0001442 based on the proportion of subjects in the EGT0001442 group reaches the American Diabetes Association (ADA) target HbA1c of <7% compared with placebo
- To assess the effect of EGT0001442 on systolic and diastolic blood pressure compared with placebo
- To assess the effect of EGT0001442 on body weight compared with placebo
- To assess the change in HbA1c change over time, week 1 to week 96
- To assess the safety of EGT0001442 in patients with T2DM

Study Design:

A multinational, 2 arm parallel groups, randomized, double-blind placebo-controlled study to compare the treatment of once daily EGT0001442 at 30 mg with matching placebo in treatment-naïve type 2 diabetic patients (i.e. not taking an antihyperglycaemic agent for ≥16 weeks prior to study entry) or with diet and exercise in combination with one oral antidiabetes drug and an HbA1c of 7-10%. Approximately 300 eligible subjects will start a 2-week placebo run-in period prior to being randomly assigned to either once daily EGT0001442 or placebo in a 1:1 ratio for 24 weeks. Subjects with hyperglycemia may receive approved anti-diabetic medication. At week 24, subjects who have completed the main treatment period will continue to receive study drug until week 96. In the treatment

extension period, subjects who have elevated HbA1c will have additional antidiabetic therapy added to the study drug consistent with treatment recommendations for type 2 diabetes.

Study Population and main eligibility criteria:
Approximately 300 patients that are inadequately controlled by diet and exercise or by treatment with a single oral anti-diabetes agent, randomized 1:1 to placebo and EGT0001442

- Type 2 diabetes per the American Diabetes Association criteria
- Male or female
- Age ≥ 18 years
- Receiving one or no oral anti-diabetic agent and diet and exercise instruction
- HbA1c between 7 and 10% at screening
- Body mass index (BMI) ≤ 37 kg/m^2
- Fasting plasma glucose <250 mg/dL at screening for subjects not treated with oral anti-diabetic therapies
- Fasting plasma glucose <240 mg/dL at screening for subjects treated with anti-diabetic therapies
- Fasting plasma glucose <250 mg/dL for all subjects at randomization

Test Product, Dose, and Mode of Administration:
EGT0001442 tablets 30 mg once daily by mouth

Reference Therapy; Dose; and Mode of Administration:

- Placebo – once daily by mouth

Duration of Treatment:

- 98 week (2wk run-in, 24 week primary evaluation, 72 week extension)

Statistical Methods:
The primary objective of this trial is to assess the efficacy of EGT0001442 in treatment-naïve type-2 diabetic patients or patients on a single oral anti-diabetic drug in combination with diet and exercise with an HbA1c between 7 and 10%. Efficacy is defined as a significant reduction in HbA1c at week 24 when compared to placebo. The effect of EGT0001442 on fasting glucose, blood pressure, body weight and the general safety of EGT0001442 in patients with T2DM will also be explored.

Statistical analyses and summaries of safety and tolerability will be performed using SAS® software (SAS Institute, Cary, NC). In all cases, significance will be judged at the α=0.05 level. No multiplicity adjustment will be required for the single primary endpoint.

Date of Original Approved Protocol: 02 February 2011

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	American Diabetes Association
AE	adverse event
ALB	albumin
ALT	alanine aminotransferase
AP	alkaline phosphatase
AST	aspartate aminotransferase
AUC_{0-24}	area under the curve from 0 to 24 hours
BMI	body mass index
BUN	blood urea nitrogen
Ca	calcium
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
Cl	chloride
C_{max}	observed maximum concentration
CRF	case report form
CRO	Contract Research Organization
CV	coefficient of variation
CVA	cerebral vascular accident
DSMB	Data and safety monitoring board
EC	ethics committee
ECG	electrocardiogram
eGFR	estimating glomerular filtration rate
FDA	Food and Drug Administration
FPG	fasting plasma glucose
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide-1

GGT	gamma glutamyl transferase
HbA_{1c}	glycosylated hemoglobin A1c
Hct	hematocrit
HDL-C	high density lipoprotein cholesterol
Hgb	hemoglobin
HIPAA	Health Information Portability and Accountability Act
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonisation
IND	Investigational New Drug
IRAE	Immediately Reportable Adverse Event
IRB	Institutional Review Board
ITT	intent-to-treat
IVRS	Interactive voice response system
LDH	lactic dehydrogenase
LDL-C	Low density lipoprotein cholesterol
MACE	Major Adverse Cardiovascular Event
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MDRD	Modification of Diet in Renal Disease
NOAEL	No observable adverse effect level
NYHA	New York Heart Association
OAM	oral anti-diabetic medications
PD	pharmacodynamics
PK	pharmacokinetics
PP	per protocol
PT	prothrombin
RBC	red blood cell (count)
SAD	single ascending dose

SAE	serious adverse event
SD	standard deviation
SMBG	self monitored blood glucose
T2DM	type 2 diabetes mellitus
TEAEs	Treatment emergent adverse events
t_{max}	time to maximum concentration
UGE_{0-24}	urinary glucose excretion from 0 to 24 h post dose
ULRR	Upper Limit of the Reference Range
USP/NF	The United States Pharmacopeia–National Formulary
UTI	urinary tract infections
WBC	white blood cell (count)
WHODRUG	World Health Organization Drug Dictionary
WOCBP	Women of childbearing potential

1 INTRODUCTION

Diabetes mellitus, characterized by hyperglycemia, is caused by defective insulin secretion, resistance to insulin action, or a combination of both. Approximately 285 million people worldwide, or 6.6%, in the age group 20-79 have diabetes in 2010. The prevalence of diabetes is projected to be 438 million or 7.8% of the adult population by 2030 (Sicree et al., 2010). Over 90% of diabetic patients have type 2 diabetes mellitus (T2DM) and over 80% of the type 2 diabetic patients are overweight or obese. Several classes of agents for type 2 diabetes are available for treating hyperglycemic conditions including insulin secretagogues, PPARγ agonists, metformin, alpha glucosidase inhibitors, glucagon-like peptide 1 (GLP-1) analogues, and dipeptidyl peptidase 4 (DPP4) inhibitors. Insulin and its analogues also are prescribed for the treatment of type 2 diabetes as the disease progresses. However, a rapid rise in the number of adult type 2 diabetics has led to an increasing recognition that additional therapeutic modalities are needed to provide safe and effective reductions of elevated plasma glucose levels.

The renal Na+/glucose transporter SGLT2 (gene name SLC5A2) is a member of a sugar transporter family that actively transports extracellular hexoses into cells using the driving energy of the transmembrane electrochemical potential for sodium ions. Individuals with disruptions in the gene encoding SGLT2 exhibit prominent glucosuria in the absence of significant comorbidities (Santer et al., 2003; van den Heuvel et al., 2002). Significantly, neither hypoglycemia nor an increased incidence of urinary tract infections have been reported in these individuals. The elimination of glucose from the blood via urinary excretion has the potential to improve both fasting and postprandial hyperglycemia without increasing insulin secretion, causing weight gain, or inducing hypoglycemia.

Phlorizin, a natural product inhibitor of SGLT1 and 2, has been shown to produce urinary glucose excretion (UGE) and lower plasma glucose levels in several animal models (Ehrenkranz et al., 2005). Development of phlorizin was discontinued due to its rapid degradation by lactase-phlorizin hydrolase and poor absorption from the gastrointestinal tract. Several SGLT2 inhibitors are in development (Han et al., 2008; Neumiller et al., 2010). Dapagliflozin is the SGLT2 inhibitor with the most extensive clinical data. Early phase studies demonstrated sustained, dose-dependent glucosuria over 24 hours with once daily oral dosing (Komoroski et al., 2009a; Komoroski et al., 2009b). A double blind, placebo controlled study showed that treatment with dapagliflozin for 6 months resulted in 0.58% – 0.89% reduction of glycosylated hemoglobin A1c (HbA1c) from baseline compared with -0.23% in the placebo group with a placebo-subtracted changes in weight up to 1.1 kg (Ferrannini et al., 2010). Increased numbers of urinary tract and genital infections were observed in the treated groups.

1.1 EGT0001442 for the treatment of type 2 diabetes mellitus

EGT0001442, a candidate oral antidiabetic agent, is a potent, highly specific inhibitor of the renal Na+/glucose transporter SGLT2. It is a benzylbenzene C-glycoside of the same

chemical structural class as dapagliflozin. EGT00001442 elicits a prominent and predictable glucosuria in laboratory animals and in healthy and diabetic subjects in clinical studies.

Several previous non-clinical and clinical studies were conducted with EGT0001474, a now-discontinued crystalline formulation of EGT0001442 and L-proline in 1:2 stoichiometry. The mass ratio of EGT0001474 to EGT0001442 is 1.5:1. In this protocol, all studies performed with EGT0001474 are described in terms of the EGT0001442 content. For example if a study used 50 mg of EGT0001474 it is described as 33 mg of EGT0001442 (delivered as proline cocrystal). EGT0001474 and EGT0001442 have similar solubility in water, similar dissolution rates when formulated as capsules, and show similar exposure in rat, monkey, and human studies.

1.1.1 Summary of non-clinical data with EGT0001442

The potential adverse effects of EGT0001442 have been evaluated through safety pharmacology, genotoxicity, acute, chronic, and reproductive toxicity studies. Repeat dose toxicity studies performed in rats, dogs and monkeys found diarrhea and gastric irritation including sporadic ulceration, at the lowest observable effect level. The NOAELs based on these studies are 6.7 and 20 mg/kg/day in rats and monkeys, respectively, representing safety multiples of 8.1 and 19.6 relative to anticipated exposures in diabetic patients at the planned clinical dose of 20 mg/day. Chronic exposures produced similar toxicity profiles, with the additional finding of microvacuolization of renal cortical cells in monkeys after 39 weeks dosing. This microscopic pathology occurred without clinical chemistry correlates, and the renal effects generally reversed during the recovery phase. EGT0001442 does not affect fertility or in utero development up to the maximum tolerated doses in rats and rabbits. Details of the toxicology findings are described in the Investigator's Brochure.

1.1.2 Summary of Clinical data with EGT0001442

Clinical studies have been conducted to evaluate safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), metabolism, and efficacy of EGT0001442. No deaths or study drug related serious adverse events (AEs) have been reported in the clinical trials. EGT0001442 up to 100 mg for up to 14 days was safe and tolerated in healthy volunteers. In a phase 2, double-blind, placebo-controlled study, subjects with type 2 diabetes mellitus were treated with EGT0001442 in doses of 5 to 50 mg or a placebo for 28 days. The most frequently occurring AEs were headache (4% in the placebo and 11% in the treatment groups), pollakiuria (none in the placebo and 4% in the treatment groups), fatigue (7% in the placebo and 2% in the treated group), and nausea (4% in the placebo and 3% in the treated group). No hypoglycemia was reported. Genital and urinary tract infections were observed in some subjects in the EGT0001442 treated groups, including balanitis candida, urinary tract infection, bacterial vaginitis, vulvovaginal candidiasis, and vulvovaginal mycotic infection.

Urinary glucose excretion (UGE) was measured in healthy and diabetic subjects. EGT0001442 increased UGE in a dose-dependent and saturable manner. The plateau in UGE corresponded to dosages of EGT0001442 above 20 mg/day. EGT0001442 treatment in subjects with T2DM for 4 weeks was effective in reducing FPG by 24 to 41.6 mg/dL in the

groups dosed with 5 to 50 mg/day EGT0001442. Subjects receiving EGT0001442 also had a reduction in body weight, blood pressure, and postprandial glucose compared to the changes in the placebo group. Details of the safety and efficacy information are described in the Investigator's Brochure

2 STUDY OBJECTIVES

2.1 Primary Objective(s)

The primary objective of this study is to assess the efficacy of EGT0001442 in lowering HbA1c at week 24 compared with placebo.

2.2 Secondary Objective(s)

The secondary objective(s) of this study is (are):

- To assess the efficacy of EGT0001442 in lowering FPG at weeks 2 and 24 compared with placebo
- To assess the efficacy of EGT0001442 based on the proportion of subjects in the EGT0001442 group reaches the American Diabetes Association (ADA) target HbA1c of <7% compared with placebo
- To assess the effect of EGT0001442 on systolic and diastolic blood pressure compared with placebo
- To assess the effect of EGT0001442 on body weight compared with placebo
- To assess the change in HbA1c change over time, week 1 to week 96
- To assess the safety of EGT0001442 in patients with T2DM

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

STUDY DESIGN

THR-1442-C-418 is a multinational, 2 arm parallel groups, randomized, double-blind placebo-controlled study to compare the treatment of once daily EGT0001442 at 30 mg with matching placebo in treatment-naïve type 2 diabetic patients (i.e. not taking an antihyperglycaemic agent for ≥16 weeks prior to study entry) or with diet and exercise in combination with one oral antidiabetes drug and an HbA1c of 7-10%. Approximately 300 eligible subjects will start a 2-week placebo run-in period prior to being randomly assigned to either once daily EGT0001442 or placebo, using a computer-generated allocation schedule, in a 1:1 ratio for 24 weeks. Subjects with hyperglycemia may receive approved anti-diabetic medication. At the end of week 24, subjects who have completed the main treatment period will continue to receive study drug until week 96. In the treatment extension period, subjects who have elevated HbA1c will have additional antidiabetic therapy added to the study drug consistent with treatment recommendations for type 2 diabetes. The primary analysis is to assess whether EGT0001442 is superior to placebo based on HbA1c change from baseline to week 24.

RESEARCH METHODS AND PROCEDURES

At screening visit, subjects who meet all the inclusion criteria, none of the exclusion criteria, and who consent to participate in the study will receive counseling for appropriate diet and exercise. Those who are on an oral antidiabetic medication (OAM) will discontinue the medication and receive placebo in this run-in prior for 14 ± 3 days. Eligible diabetic subjects who are treatment naïve and who control their hyperglycemia through diet and exercise will also receive placebo and the hyperglycemia will be monitored to ensure that their fasting blood glucose levels remain below 250 mg/dL during this interval of 14 ± 3 days.

After the run-in period, approximately 300 subjects will complete the baseline assessment on day 1 after overnight fasting to confirm their eligibility. The subjects that remain eligible will be randomly assigned to one of the 2 treatment groups on day 1. Randomization will be stratified by study center and based on screening HbA1c (≥7 to <8.5% or ≥8.5 to 10%). The planned doses are 30 mg/day of EGT0001442 or placebo. Each subject will be provided with study drug for 6 weeks, dosing instructions and log, diet and exercise counseling, and a diary card for recording food and fasting glucose information on the days prior to each clinic visit.

Each subject will be instructed to return to the clinic on weeks 2, 6, 12, 18, and 24 for safety monitoring and efficacy assessment including review of adverse events, concomitant medication, ECG, vital signs, physical examinations, testing of blood chemistry and hematology laboratory parameters, and a urinalysis.

Subjects who complete the 24-week treatment period will continue receiving the study drug for an additional 72 weeks. Subjects who receive rescue medication due to poor glycemic

control will continue to receive approved anti-diabetic medications and standard of care per investigator decision according to current treatment guidelines for 72 weeks. In the treatment extension period, subjects must return to the clinic on weeks 36, 48, 60, 72, 84, and 96 for continuous safety monitoring and efficacy assessment, including review of HbA1c values, adverse events, concomitant medication, ECG, vital signs, and physical examinations. A follow up exit visit will be conducted at 1 week after the last dose. Subjects will be advised to see their primary physician and resume standard of treatment to control diabetes.

GLYCEMIC CONTROL

During the run-in period, subjects will be instructed to determine daily self-monitored blood glucose (SMBG) after an overnight fast. The SMBG record will be reviewed by the investigator at each clinic visit. If the fasting blood glucose is > 216 mg/dL (12 mmol/L) in two consecutive days, the subject should contact the clinical staff. In addition, subjects will be instructed that they must contact the clinic within 24 h if SMBG is ≥ 270 mg/dL (15 mmol/L). If the fasting SMBG is ≥ 270 mg/dL (15 mmol/L) without explanations for the elevation, the investigator will review the SMBG record and determine if the subject should attempt to improve diet and exercise to maintain glycemic control or if the subject must discontinue from the study and resume diabetic medications. Subjects with symptomatic hyperglycemia or hypoglycemia should be withdrawn if the symptoms are severe.

During the 24-week main treatment period, study subjects will be advised to continue daily SMBG measurements and contact the clinic if the SMBG is ≥270 mg/dL (15 mmole/L) from week 1 (week of randomization) to week 6, ≥240 mg/dL (13.3 mmole/L) from week 6 to week 12, or ≥200 mg/dL (11.1 mmole/L) from week 12 to week 24. During the 72-week extension period (weeks 25 to 96), subjects will continue to monitor the SMBG and contact the clinic if SMBG is ≥200 mg/dL (11.1 mmole/L). Values of HbA1c will be evaluated in the extension period by the investigator and approved standard of oral therapy will be prescribed if HbA1c is elevated.

The investigator must review the SMBG record and FPG values in every clinic visit and assess whether any subject should receive rescue medications to treat the hyperglycemic condition during the 24-week main treatment period. The subject must be queried to assess compliance with a minimum of a 10 h fast prior to blood draw to ensure the FPG values can be accurately determined. If a subject has not fasted for 10 h, the subject must return within a week after proper fasting. The investigator will provide diet and exercise counseling and determine if the subject should receive additional rescue medication as a result of the glucose. A serum sample must be drawn prior to the rescue medication so that the last HbA1c value while the subject is on study drug only can be carried forward to 24 weeks for the primary end point analysis.

OTHER SAFETY MONITORING ACTIVITIES

The safety monitoring activities will include vital signs, physical examinations, urinalysis, adverse events, and concomitant medication use. The occurrence of blood, liver, or skin disorders will be monitored through laboratory testing and adverse event documentation.

Adverse event of special interests will include any clinical signs and symptoms indicating either upper or non-upper urinary tract infections (UTIs) and genital infections. Any adverse events that mapped to UTIs or genital infections must be documented.

DATA AND SAFETY MONITORING BOARD (DSMB)

An independent Data and Safety Monitoring Board (DSMB) will monitor the overall safety information during the EGT0001442 development. The safety review activity and potential risk benefit assessment will be defined in the charter.

MAJOR ADVERSE CARDIOVASCULAR EVENT ADJUDICATION

An independent cardiovascular adjudication committee is established to review the cardiovascular events during the study in a blinded fashion. These events include cardiovascular mortality, myocardial infarction, stroke, and hospitalization for acute coronary syndromes, urgent revascularization procedures, and, other possible serious cardiovascular events. The adjudicated events will be documented and archived to allow a meta-analysis to be performed to assess if there is any increase of cardiovascular risk to an unacceptable extent at the time of completion of all phase 3 clinical studies.

3.2 Rationale for Study Design and Control Group

THR-1442-C-418 is designed to evaluate the efficacy of EGT0001442 in the treatment of patients with T2DM. A randomized, double-blind study is the most suitable design and placebo is the appropriate control to evaluate a new agent in diabetic subjects. Diet and exercise counseling during the entire study will be provided to all participating subjects to reduce risks of worsening diabetic conditions. Monitoring plan based on SMBG, FPG, and HbA1c measurements as well as criteria to initiate rescue medications are included in the protocol to prevent prolonged hyperglycemia.

Results from published data in individuals with genetic mutations in the gene encoding SGLT2, subjects that have been treated with other SGLT2 inhibitors, and from previous clinical studies in healthy or diabetic subjects treated with EGT0001442 indicate that the risk of induced hypoglycemia as a consequence of the loss of SGLT2 activity should be minimal.

Reduction in HbA1c directly reflects improvement in glycemic control and is considered a well validated surrogate for the long-term microvascular complications of diabetes mellitus. Results from study THR-1442-C-402 demonstrated that 4 weeks of treatment resulted with a dose dependent reduction of 24 – 42 mg/dL FPG in subjects receiving EGT0001442 5 – 50 mg per day. Thirty (30) mg/ day of EGT0001442 dosage was chosen in the proposed study based on the near saturation of UGE and FPG decrease in previous clinical studies in healthy or diabetic subjects. Clinical data in the previous studies indicated that 30 mg/day EGT0001442 is well tolerated.

3.3 Study Duration and Dates

In the proposed study, diabetic subjects will be screened within 3 weeks of washout start. Eligible subjects who sign the written consent will receive placebo and start a 2 week run-in period prior to study drug administration. Subjects will receive 24 weeks of treatment for the main efficacy study and will continue for an additional 72 weeks for additional safety and efficacy study. All subjects will be followed for 1 week after the last dose. The overall study duration from screening until follow-up could last a maximum of 102 weeks for the study subjects. The duration of the overall study depends on the rate of patient accrual. For details of the schedule and nature of the investigations, see the Trial Activities Charts in Appendix 1

4 STUDY POPULATION SELECTION

4.1 Study Population

The study population will include approximately 300 subjects diagnosed with T2DM that are inadequately controlled by diet and exercise or by treatment with a single oral anti-diabetes agent and have the HbA1c between 7% and 10%. The study will recruit subjects from approximately 50 trial centers in 3 countries.

4.2 Inclusion Criteria

1. Male or female subjects ≥18 years old
2. Diagnosed with type 2 diabetes
3. Body mass index (BMI) ≤ 37 kg/m^2
4. HbA1c between 7 and 10% (inclusive) at screening based on an upper limit of normal for the HbA1c assay being 6.5±0.2 %
5. FPG <250 mg/dL at screening for subjects not treated with oral anti-diabetic therapies or FPG <240 mg/dL at screening for subjects treated with anti-diabetic therapies
6. Diabetes currently treated with diet and exercise only or diet and exercise along with one approved oral anti-diabetic agent
7. If taking anti-diabetic medication, dose and regimen must be stable for past 3 months
8. If taking antihypertensive medication, dose and regimen must be stable for past 3 months
9. If taking lipid modifying therapy, dose and regimen must be stable for past 3 months
10. Blood glucose <250 mg/dL based on finger stick blood glucose for all subjects at randomization
11. Subjects willing and able to comply with the investigational nature of the study and able to communicate well with investigators.
12. Able to comprehend and willing to provide written informed consent in accordance with institutional and regulatory guidelines.

4.3 Exclusion criteria

Subjects meet any of the criteria will be excluded:

1. Hemoglobinopathy that affects HbA1c measurement
2. Current use of injected therapy for treatment of diabetes (insulin or GLP-1 receptor based therapy)
3. Genitourinary tract infection within 6 weeks of screening
4. Greater than 2 episodes of genitourinary tract infection in the past year
5. History of kidney stones, bladder malfunction or other significant risk factor for urinary tract infections

6. eGFR, as calculated by the modification of diet in renal disease study equation (MDRD), < 50 mL/min/1.73 m^2 (Appendix 2)
7. Abnormal tests of liver function ALT, AST or bilirubin ≥ 3x ULRR
8. Diagnosed with proliferative retinopathy
9. Uncontrolled hypertension (blood pressure >150/95)
10. Not willing to use effective birth control if female with child-bearing potential
11. Female subjects who are pregnant or nursing
12. Life expectancy < 2 years
13. New York Heart Association (NYHA) Class 4 heart failure
14. Sera positive of HCV, HIV, or positive on drug screen
15. Currently participating another interventional trial
16. Not able to comply the study scheduled visits

5 STUDY TREATMENT(S)

5.1 Description of Treatment(s)

5.1.1 Study Drug

Theracos, Inc. will provide EGT0001442 tablets in one of the four different strengths as follows:

10 mg SR formulation (EGT0001442 SR Tablet, 10 mg)
15 mg SR formulation (EGT0001442 SR Tablet, 15 mg)
20 mg SR formulation (EGT0001442 SR Tablet, 20 mg)
20 mg IR formulation (EGT0001442 IR Tablet, 20 mg)

The SR tablet formulations consist of EGT0001442 (active pharmaceutical ingredient) and excipients including HPMC, lactose monohydrate, sodium bicarbonate, colloidal silicon dioxide and magnesium stearate in the 10, 15, and 20 mg dosages. The IR tablet formulation consists of 20 mg EGT0001442 (active pharmaceutical ingredient) and excipients including microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate.

All study drug supplies will be prepared and labeled according to the requirements of local law and legislation and will be kept in a secure storage facility at controlled room temperature, 15 – 30°C (59 – 86°F). The pharmacist or designated CRO personnel will dispense the study drugs for each subject according to randomization assignment made in the IVRS.

5.1.2 Placebo

Theracos, Inc. will provide placebo tablets. The placebo control tablets consist of HPMC, lactose monohydrate, sodium bicarbonate, colloidal silicon dioxide and magnesium stearate.

Placebo will be prepared in white opaque tablets of the same size and appearance as the active drug tablets. All placebo supplies will be prepared and labeled according to the requirements of local law and legislation and will be kept in a secure storage facility at controlled room temperature, 15 – 30°C (59 – 86°F). The placebo control is packaged in a manner identical to the active drug product. The placebo tablets will be administered identically to the EGT0001442 tablets.

5.1.3 Rescue medications

Approved anti-diabetic medications will be provided to subjects who met the criteria to receive rescue medication due to poor glycemic control.

5.2 Treatments Administered

Study drug will be provided to the pharmacist in bottles of 45 tablets per bottle. Individual bottles of placebo will be provided for the run-in portion of the study. For the first 24 weeks of the study, subject kits will be provided and each kit will contain 4 bottles containing 45 tablets per bottle. For study weeks 25 – 96, subject kits will contain 2 bottles of 45 tablets. Study drug, EGT0001442 10, 15, or 20 mg tablets or matching placebo, will be dispensed by the pharmacy or designated study staff every 6 - 12 weeks. There will be no intra-subject dose escalation or back-titration.

Subjects who require rescue medication due to hyperglycemia will receive standard care for treating type 2 diabetes in addition to the study drug. The pharmacist will dispense the medications per investigator's prescription.

5.3 Selection and Timing of Dose for Each Patient

Dosing with either active drug or placebo will be based on randomized assignment. All study subjects will be instructed to self-administer one capsule prior to breakfast once daily and complete the dosing log. Subjects will be advised to take the study medication with a glass of water. The tablets will be swallowed without chewing.

On the day of scheduled clinic visits, subjects must fast for a minimum of 10 h prior to the visits at which blood samples will be drawn. During fasting, only water will be permitted. Subjects will be asked to record the meals they consume and the time that they last ate prior to blood draw for FPG and other laboratory testing.

5.4 Method of Assigning Patients to Treatment Groups

Eligible subjects who complete the 14 ± 3 day washout period to verify eligibility for the study and stability of their diabetes will be randomized to receive EGT0001442 or placebo according to a randomization code. Subjects are assigned to placebo or EGT0001442 at 30 mg/day in a 1:1 ratio. The random assignment of study subjects to treatment groups will be centrally located and managed utilizing an Interactive Voice Response Systems (IVRS). Randomization will be stratified by study center and based on screening HbA1c (≥7 to <8.5% or ≥8.5 to 10%). This randomization protocol is designed to balance experimental treatments within each center and the baseline HbA1c.

The study will be conducted at multiple investigative sites and will likely involve variable numbers of subjects at each site. Enrollment will be on a competitive basis but will be capped at 30% of the total randomized subjects (90 subjects) from one center.

5.5 Blinding

The study drug will be blinded to the sponsor, investigators, study coordinators, pharmacists, study subjects, and the cardiovascular adjudication committee members. Upon randomization, each subject will receive a subject randomization number and a drug kit

assigned to the subject. To maintain blinding of the treatment, the values of the HbA1c after dosing starts will remain blinded to all study personnel and patients until all subjects have completed the 24 week treatment period.

If knowledge of the test substance is needed to manage the subject's condition, the investigator will contact the IVRS to obtain the treatment assignment. If unblinding occurs, the time and reason for unblinding will be recorded on the CRF and the sponsor must be notified within 24 h.

A designated statistician who is not involved with the study operation will hold the treatment code. The unblinded treatment information can be provided to the DSMB to facilitate the evaluation of any clinically important increase in the rate of a serious suspected adverse reaction or to the designated safety contact when the treatment information is required to determine if an expedited safety report must be submitted to regulatory agencies. The treatment code will be unblinded when the clinical database is locked and data are to be analyzed.

The treatment assignment will continue to be withheld from the cardiovascular adjudication committee members at the conclusion of the study until all phase 2 and phase 3 investigational studies are completed and a meta-analysis to assess cardiovascular risk is conducted.

5.6 Concomitant Therapy

Medications to control blood pressure, specified lipid lowering drugs, and aspirin are allowed during the study period. Allowed anti-hypertensive medications include ACE inhibitors, angiotensin receptor blockers, calcium channel blockers, beta blockers and diuretics. The antihypertensive medications should continue for 24 weeks without changing unless clinically indicated. In the extension period, the investigators should evaluate the blood pressure of each subject and determine if adjustment of the anti-hypertension drug should be adjusted per guideline.

Subjects may receive any medications for adverse events that are necessary in the investigators' judgment. Subjects are permitted to take their prescription medications or medicinal supplements.

Concomitant medications administered at the time of randomization and during the study are to be recorded on the CRF. The medication name, dose, frequency, route of administration, date(s) of administration and reason for administration must be recorded. Glucose for the treatment of hypoglycemia will be considered concomitant medication and must be recorded on the CRF. This documentation should continue through the treatment period and the follow up period. Medications that a subject receives after enrollment to the study and prior to randomization must be recorded in the CRF.

5.7 Restrictions

5.7.1 Prior Therapy

Medications for controlling diabetes, hypertension, hyperlipidemia, and aspirin as specified in the eligibility criteria are allowed as prior therapy. No subject shall have been treated with an investigational drug within 30 days or 7 half lives, nor have used steroids within 14 days prior to the first dose of study medication. Use of acetaminophen or multivitamins in this interval is permitted.

5.7.2 Fluid and Food Intake

Enrolled diabetic subjects will receive counseling regarding an appropriate diet to achieve glycemic control based on standards of medical care in diabetes (ADA, 2008). The diet should be low in saturated fat, high in fiber, and low in simple carbohydrates and contain appropriate caloric intake to maintain weight.

Subjects will fast for a minimum of 10 h prior to any of the visits at which blood samples will be drawn. During fasting, only water will be permitted. Subjects will be asked to record the meals they consume and the time that they last ate prior to blood draw for FPG and other laboratory testing.

5.7.3 Patient Activity Restrictions

Throughout the study period, subjects are advised to perform at least 150 min/week of physical activity that is appropriate for their physical condition.

5.8 Treatment Compliance

To ensure the treatment compliance, subjects will be provided with dosing instruction and a dosing record. The dosing record will be reviewed with the study staff during each visit and drug accountability will be performed and recorded at the end of the treatment period for each subject.

Approximately 0.5 mL plasma sample will be collected and stored at -20^{o}C at each clinic visit during the treatment period. The samples will be shipped to the analytical laboratory in batches. EGT0001442 plasma concentration may be determined from all or a portion of the samples to verify the drug exposure. The results of the analysis will not be disclosed to the study team during the 24 week main treatment period until the clinical data for the primary analysis are locked.

5.9 Packaging and Labeling

5.9.1 Study drug for main treatment period

EGT0001442 tablets and placebo are packaged in high density polyethylene (HDPE) bottles sealed with a child resistant closure. Each kit will include 4 bottles of study drug. The product is packaged with 45 tablets per bottle including a 3 tablet overage in each bottle for accidental loss of study drug during the treatment period between visits.

Study drug bottles will be labeled with the protocol number, product identification, lot number, kit number, Sponsor's name and address, and the investigational drug caution statement.

5.9.2 Study drug for the treatment extension period

The study drug EGT0001442 tablets and placebo are packaged in HDPE bottles sealed with a child resistant closure. Study drug bottles will be labeled with the protocol number, product identification lot number, the sponsor's name and address, and the investigational drug caution statement.

5.10 Storage and Accountability

EGT0001442 tablets and matching placebo will be stored at controlled room temperature, 15 – 30°C (59 – 86°F). The rescue medications will be stored in conditions specified in the manufacturers' labeling information.

5.11 Investigational Product Retention at Study Site

The investigational products should be stored in a secure area with limited access. The drug storage facility must comply with the medication storage instructions. EGT0001442 or placebo should be stored at controlled room temperature until ready for dispensing to study subjects. The trial staff must record the amount of investigational product dispensed to each subject on the dosing record. To ensure adequate record keeping, subjects must return all trial products at the end of the treatment period and the remaining tablets will be accounted for in the CRF and drug accountability forms provided. The procedures for obtaining drug resupply will be provided by the sponsor. At the completion of the trial, all used and unused bottles must be destroyed after drug accountability is verified by Theracos or its designee.

6 STUDY PROCEDURES

6.1 Informed Consent

All subjects will be informed of the nature and purpose of the study and their written informed consent will be obtained during the pre-study screening procedures conducted within three weeks prior to the start of the run-in period. A copy of the Informed Consent form, including subject information, will be provided to each subject in his native language.

6.2 Medical History

The following information will be collected at the screening period:

- Demographic information including age, sex, race, and whether a female subject is of childbearing potential or not
- Significant medical, surgical history with dates.
- History of kidney stones, bladder malfunction, or frequent urinary tract infections
- Incident of genitourinary tract infections in the previous 6 weeks
- History of smoking, alcohol or drug dependence or abuse
- History of diagnosis with HIV sero-positive acquired immunodeficiency syndrome (AIDS) or Hepatitis B/C
- Use of any investigational drug in the previous 30 days or seven half-lives, whichever is longer
- Prior treatment with EGT0001474 or EGT0001442. Currently participating another interventional trial or not.
- Use of aspirin, and use of cholesterol-lowering drugs and any other medications including over the counter drugs, vitamins, or dietary supplements within 14 days
- Type of diabetes and time of first diagnosis
- Anti- diabetic or hypertension medication history
- History of cardiovascular events including angina, hypertension, congestive heart failure, atherosclerotic cardiovascular disease, myocardial infarction and diagnosis based on the New York Heart Association class, peripheral edema, and cerebrovascular ischemia (TIA or CVA).
- History of cardiac procedures including any re-vascularization procedures or hospitalization for chest pain.

6.3 Physical Examination

A complete physical examination will be performed by the investigator at screening and at the termination visit. A complete physical examination will include measurement of body weight and height (height will be measured only at screening), general assessment of all body systems including the skin, head, eyes, ears, nose, throat, neck, thyroid, lungs, heart, abdomen, lymph nodes, and extremities.

An abbreviated physical examination will include body weight and general assessment of the skin, heart, lungs and abdomen. Abbreviated physical examinations will be performed by the investigator at all other time points, unless clinically indicated.

The body weight must be determined using a scale that is calibrated regularly and no less than annually.

6.4 Vital Signs

Vitals signs include pulse, systolic and diastolic blood pressure at sitting position after a subject has been sitting for 5 minutes, respiration rate, and temperature. Vital signs must be taken twice with at least 3 minutes apart.

6.5 Electrocardiography

A 12-lead electrocardiogram (ECG) will be conducted as listed in study activity chart in Appendix 1 and whenever clinically indicated.

6.6 Diet and exercise counseling

Enrolled diabetic subjects will receive counseling regarding an appropriate diet to aid in glycemic control based on standards of medical care in diabetes throughout the study (ADA, 2008).

6.7 Clinical Laboratory Tests

6.7.1 Laboratory Parameters

Subjects will be in a seated or supine position during blood collection. Schedule of each laboratory test is outlined in Appendix 1. Clinical laboratory tests will include the following:

Table 1. List of Laboratory Tests

Hematology:	Serum Chemistry:
- Hematocrit (Hct)	- Albumin (ALB)
- Hemoglobin (Hgb)	- Alanine aminotransferase (ALT;
- Platelet count	- Aspartate aminotransferase (AST;

- Red blood cell (RBC) count
- White blood cell (WBC) count with differential

Urinalysis:

- Appearance
- Bilirubin
- Color
- Glucose
- Ketones
- Microscopic examination of sediment
- Nitrite
- Occult blood
- pH
- Protein
- Specific gravity
- Urobilinogen

Hepatitis screening HBsAg, HBcAg, and HCV

Urine drug screen

Urine human chorionic gonadotropin (hCG) (only for females who are not diagnosed as postmenopausal)

- Blood urea nitrogen (BUN)
- Calcium (Ca)
- Carbon dioxide (CO_2)
- Chloride (Cl)
- Creatinine
- Glucose
- Phosphorus
- Potassium (K)
- Sodium (Na)
- Magnesium
- Total bilirubin
- Direct bilirubin
- Total cholesterol
- High density lipoprotein cholesterol (HDL-C)
- Low density lipoprotein cholesterol (LDL-C, calculated)
- ApoB
- Total protein
- Triglycerides
- Uric acid
- Fasting plasma glucose
- HbA1c

Coagulation:

- Prothrombin time (PT)

6.7.2 Sample Collection, Storage, and Shipping

6.7.2.1 Hematology and blood chemistry

Blood samples for hematology, coagulation, and chemistry will be collected. Timing of collection is described in the Schedule of Events (see Appendix 1).

The study staff will contact each subject prior to a scheduled clinic visit to confirm the time of the visit and to remind the subject of appropriate diet and exercise control, proper fasting, and to record the diary card with meals of the day and time that the subject ate prior to the

clinic visit. A subject must be queried to assess compliance with a minimum of a 10 hour fast prior to blood draw to ensure the FPG and triglycerides values can be accurately determined. If a subject has not fasted for 10 hours, the subject must return as soon as can be arranged (within 7 days) after proper fasting. If the 10 h fast is not collected within 7 days of the visit, the fasting plasma glucose will be considered missing.

6.7.2.2 Urinalysis

Clean-catch, midstream urine samples will be collected per schedule outlined in Section 7.

Dipstick urinalysis will be conducted. Microscopy will be conducted if the subject has a positive result on any of the dipstick tests that require microscopic follow-up to clarify their significance.

6.8 Dispensing Study Drug

Study drug will be dispensed by the pharmacist or designated personnel on day 1 with self administered dosing instructions and a dosing log.

6.9 Adverse Events Assessments

6.9.1 Definitions

An adverse event (AE) is defined as any new medical problem, or exacerbation of an existing problem, experienced by a subject while enrolled in the study, whether or not it is considered drug-related by the investigator.

A serious adverse event (SAE) includes any event that results in any of the following outcomes:

- death
- life-threatening, i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.
- persistent or significant disability/incapacity
- requires in-patient hospitalization or prolongs hospitalization
- congenital anomaly/birth defect
- other medically significant events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above, e.g., allergic bronchospasm requiring intensive treatment in an emergency room or home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

Non-serious adverse events are all events that do not meet the criteria for a "serious" adverse event.

Immediately Reportable Adverse Event (IRAE): Any serious adverse event or any adverse event that necessitates discontinuation of study drug, including pregnancy.

Clinical Laboratory Changes: It is the investigator's responsibility to review the results of all laboratory tests as they become available. For each abnormal laboratory test result, the investigator needs to ascertain if this is an abnormal (i.e., clinically significant) change from baseline for that individual subject. (This determination, however, does not necessarily need to be made the first time an abnormal value is observed. The investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests). If this laboratory value is determined to be an abnormal change from baseline for that subject, this is considered an AE.

High serum or plasma glucose (hyperglycemia) and high HbA1c, the disease related morbidity, are being followed as the study endpoints and will not be documented as adverse events. If, however, the event fulfills any of the criteria for a "serious" adverse event, it must be recorded and reported as such.

Hypoglycemia will be defined as any FPG or SMBG value < 70 mg/dL.

Any increase in liver function tests (AST, ALT, or bilirubin) greater than 3X the ULN for the laboratory utilized will be considered a clinical laboratory adverse event.

Increase in creatinine from baseline by 0.5 mg/dL or more will be reported as a laboratory adverse event.

Severity: Adverse events will be graded on a 3-point scale and reported as indicated on the CRF. The intensity of an adverse experience is defined as follows:

1 = Mild: Discomfort noticed, but no disruption to daily activity.
2 = Moderate: Discomfort sufficient to reduce or affect normal daily activity.
3 = Severe: Inability to work or perform normal daily activity.

Study Drug Causality: Relationship of an adverse event to treatment will be assessed as follows:

- Definite: There is a reasonable causal relationship between the study drug and the AE, when the event responds to withdrawal of the study drug (dechallenge), and recurs with rechallenge by administration of the study drug.
- Probable: There is a reasonable causal relationship between the study drug and the AE. The event responds to dechallenge. Rechallenge not required.
- Possible: There is a reasonable causal relationship between the study drug and the AE. Dechallenge is lacking or unclear.

- Not Likely: There is a temporal relationship to study drug administration, but there is not a reasonable causal relationship between the study drug and the event.
- Unrelated: There is not a temporal or causal relationship to the study drug administration.

6.9.2 Eliciting and Reporting Adverse Events

The investigator will periodically assess subjects for the occurrence of adverse events. In order to avoid bias in eliciting adverse events, subjects should be asked the following non-leading question: "How have you felt since your last visit?" All adverse events (serious and non-serious) reported by the subject must be recorded on the source documents and CRFs provided by the sponsor.

In addition, Theracos or its designated personnel must be notified immediately by telephone or fax of any immediately reportable adverse events according to the procedure outlined below. Special attention should be paid to recording hospitalization and concomitant medications.

6.9.3 Immediately Reportable Adverse Events (IRAE)

The investigator must report any serious adverse event or pregnancy, by telephone or by fax to Theracos immediately after the investigator becomes aware of the event. An Immediately Reportable Adverse Event (IRAE) form should be completed and sent by fax or overnight courier to the sponsor within 24 hours of knowledge of the event by the site.

Non-serious events that require discontinuation of study drug (including laboratory abnormalities) should be reported to Theracos within 3 working days. The IRAE form should be completed and sent by fax or overnight courier to the sponsor.

Subjects experiencing serious adverse events should be followed clinically until their health has returned to baseline status or until all parameters have returned to normal, or have otherwise been explained. It is expected that the investigator will provide or arrange appropriate supportive care for the subject.

6.9.4 Pregnancy

Women of childbearing potential (WOCBP) who are sexually active must use an effective method of birth control during the course of the study, in a manner such that risk of failure is minimized. Unless the subject and his/her partner(s) are sterile (i.e., women who have had a hysterectomy or have been postmenopausal for at least 12 consecutive months) or remain abstinent, two of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device (IUD), birth control pills, birth control implant, condom or sponge with spermicide. Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy.

Before enrolling WOCBP in this clinical trial, investigators must review guidelines about study participation for WOCBP. The topics should generally include:

- General information
- Informed consent form
- Pregnancy prevention information
- Drug interactions with hormonal contraceptives.
- Contraceptives in current use.
- Guidelines for the follow-up of a reported pregnancy.

Prior to study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. The subject must sign an informed consent form stating that the above-mentioned risk factors and the consequences were discussed with her.

During the study, all WOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual cycle).

If a subject or investigator suspects that the subject may be pregnant prior to study drug administration, the study drug administration must be withheld until the results of blood and urine pregnancy tests are available. If the pregnancy is confirmed, the subject must not receive the study drug and must not be enrolled in the study. If pregnancy is suspected while the subject is receiving study treatment, the study drug must be withheld immediately (if reasonable, taking into consideration any potential withdrawal risks) until the result of the pregnancy is known. If pregnancy is confirmed, the study drug will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for subject safety) and the subject withdrawn from the trial. [Exceptions to study discontinuation may be considered for life-threatening conditions only after consultations with a Theracos Medical Monitor (see Appendix III).]

The investigator must immediately notify the Medical Monitor of any female subject who becomes pregnant within 30 days after study drug exposure. The investigator must record the event on the Pregnancy Surveillance form and forward it to Theracos Clinical Drug Safety.

Protocol required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the investigator must report to Theracos, on appropriate Pregnancy Surveillance form(s), follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants will be followed for a minimum of six months.

6.9.5 Procedure for Breaking the Blind

The investigator should remain blinded of the subject treatment during the entire study UNLESS knowledge of the subject's treatment is required for the clinical care and safety. Emergency Code Break module in the IVRS is used for such emergency situations. The investigator must confirm the intention to unblind the subject's treatment to obtain the dose information. Upon completion of the unblinding, the system will send an alert to designated study team members that an unblinding event occurred. Documentation of breaking the blind should be recorded in the subject's medical record with the date and time the blind was broken, and the names of the personnel involved.

6.9.6 Follow-up of Adverse Events

6.9.6.1 Follow-up of Non-serious Adverse Events

Non-serious adverse events that are identified on the last scheduled contact must be recorded on the AE CRF with the current status noted. All non-serious events that are ongoing at this time will be recorded as ongoing on the CRF.

6.9.6.2 Follow-up of Post Study Serious Adverse Events

Serious adverse events that are identified on the last scheduled contact must be recorded on the AE CRF page and reported to Theracos according to the reporting procedures outlined in Section 6.9.3. This may include unresolved previously reported serious adverse events, or new serious adverse events. The investigator should follow these serious adverse events until the events are resolved, or the subject is lost to follow-up. Resolution means the subject has returned to the baseline state of health, or the investigator does not expect any further improvement or worsening of the subject's condition. The investigator should continue to report any significant follow-up information to Theracos up to the point the event has been resolved.

Any new serious adverse events reported by the subject to the investigator that occur after the last scheduled contact, and are determined by the investigator to be reasonably associated with the use of the study drug, should be reported to Sponsor. This may include serious adverse events that are captured on follow-up telephone contact or at any other time point after the defined study period (i.e., up to last scheduled contact). The investigator should follow serious related adverse events identified after the last scheduled contact until the events are resolved, or the subject is lost to follow-up. The investigator should continue to report any significant follow-up information to Sponsor up to the point the event has been resolved.

Any serious adverse events reported by the subject to the investigator that occur after the last scheduled visit, and are determined by the investigator to be reasonably associated with the use of the study drug, should be reported to Sponsor. This study requires that subjects be actively monitored for serious adverse events at least 14 days after discharge from the study.

6.9.7 Adverse event of special interest

6.9.7.1 Genitourinary infections

Events representing genitourinary infection (e.g. cystitis, urethritis, pyelonephritis, balanitis, vulvovaginitis should be carefully evaluated and documentation of signs, symptoms, infectious agent (bacterial or fungal), and treatment should be undertaken.

6.9.7.2 Renal and urinary disorders

Events that may be related to the diuretic effect of an SGLT2 inhibitor (e.g. nocturia, pollakiuria, polyuria, and dysuria) should be carefully evaluated and documented.

6.9.7.3 Major Adverse Cardiovascular Event (MACE)

Evaluation of major adverse cardiovascular events will be undertaken across the development program for EGT0001442. All events that potentially represent myocardial infarction, cerebrovascular accident (stroke), acute coronary syndrome, or cardiovascular death are to be evaluated by an adjudication committee.

6.9.7.4 Hypoglycemia

Severe hypoglycemia is defined as hypoglycemia with documented blood glucose 2.8 mmol/L (50 mg/dL) or symptoms that promptly resolve with oral carbohydrate, intravenous glucose, or glucagon that require the assistance of medical or paramedical personnel.

6.10 Concomitant Medication Assessments

A concomitant medication is any medication the patient enters the trial using and is expected to continue using for some portion of the trial as well as any medication the patient uses during the course of the trial. All concomitant medications recorded at trial entry must have a related concomitant illness listed under the medical history as ongoing at the time of patient entry into the trial unless the medication is an allowed treatment for the disease under study.

EGT0001442 or placebo are the study drugs and are not considered concomitant medications. The rescue medications for controlling hyperglycemia must be recorded as concomitant medications.

All prescription and over-the-counter medications patients receive pre-study and continue during the trial as well as any new medications started during the trial must be documented on the CRF. This documentation should continue until one week from the end of the last treatment.

Concomitant medications will be coded using the World Health Organization dictionary (WHODRUG). A table of concomitant medications based on the anatomic therapeutic chemical classification (ATC) and preferred name will be produced. A listing of concomitant medications will include all medications taken during the course of the study.

Any medications taken prior to the start of the study medication will be listed and summarized.

6.11 Removal of Patients from the Trial or Study Drug

The investigator may withdraw a patient from any of the following reasons:

- A protocol violation occurs,
- A serious or intolerable adverse event occurs,
- A clinically significant change in a laboratory parameter occurs,
- The sponsor or investigator terminates the study, or
- The patient requests to be discontinued from the study.

6.12 Other Study Procedures

Approximately 0.5 mL plasma sample will be collected and stored at -20^{o}C at each clinic visit during the treatment period. The samples will be shipped to the analytical laboratory in batches. EGT0001442 plasma concentration may be determined from all or a portion of the samples to verify the drug exposure.

7 STUDY ACTIVITIES

The study activities in each clinic visit are listed below and are presented in Appendix A. Screening period may last up to 21 days (Visit 1 to Visit 2), Run-in period is to be 14±3 days (Visit 2 to Visit 3), Visit 3 to Visit 4 window is 14±3 days. All other visit windows are the nominal duration from randomization ± 7 days.

7.1.1 Visit 1 - Screening (weeks –5 to -2)

The screening can be performed up to 3 weeks from the start of study activities. During the screening period, the following information will be gathered or the indicated procedure will be performed:

- Informed Consent and medical history obtained, and Inclusion/Exclusion criteria evaluated
- Complete physical examination including height and weight
- Vital Signs: blood pressure, pulse, temperature, respiratory rate taken in the sitting position after at least 5 minutes of rest. Blood pressure must be measured twice with at least 3 min apart
- 12 lead ECG taken in the supine position after at least 5 minutes of rest
- Blood draw for hematology (CBC with platelets, WBC with differential), serum chemistry including FPG, and coagulation as detailed in section 6.7.1
- Urinalysis
- Urine screen for drugs of abuse. Drug screening includes amphetamines, barbiturates, cocaine metabolites, opiates, benzodiazepines, and cannabinoids.
- Urine pregnancy test (only for females who are not postmenopausal)
- The subject must be queried to assess compliance with a minimum of a 10 h fast prior to blood draw to ensure the FPG values can be accurately determined. If a subject has not fasted for 10 h, the subject should return within a week after proper fasting.

7.1.2 Visit 2 – run-in period (day -14±3)

- Confirm eligibility
- Diet and exercise counseling
- Glucometer dispensing and training for SMBG determination
- Discontinue anti-diabetic medication
- Vital Signs: blood pressure, pulse, temperature, respiratory rate taken in the sitting position after at least 5 minutes of rest. Blood pressure must be measured twice with at least 3 min apart

- Dispense study medication for the run-in period

7.2 Primary Efficacy Phase

7.2.1 Visit 3 – procedures (Day 1 in Week 0)

- The subject must be queried to assess compliance with a minimum of a 10 h fast prior to blood draw to ensure the FPG values can be accurately determined. Only water is permitted. If a subject has not fasted for 10 h, the subject should return within a week after proper fasting.

- Confirm eligibility
- Diary and SMBG review
- Adverse events and pre-treatment medications assessment
- Randomization
- Vital Signs: blood pressure, pulse, temperature, respiratory rate taken in the sitting position after at least 5 minutes of rest. Blood pressure must be measured twice with at least 3 min apart
- 12 lead ECG taken in the supine position after at least 5 minutes of rest
- Dispense study medication based on randomization assignment
- Blood draw for hematology (CBC with platelets, WBC with differential), serum chemistry including FPG, and coagulation as detailed in section 6.7.1
- Urinalysis

7.2.2 Visit 4 – Procedures (week 2)

- The subject must be queried to assess compliance with a minimum of a 10 h fast prior to blood draw to ensure the FPG values can be accurately determined. Only water is permitted. If a subject has not fasted for 10 h, the subject should return within a week after proper fasting.

- Diary and SMBG review
- Vital Signs: blood pressure, pulse, temperature, respiratory rate taken in the sitting position after at least 5 minutes of rest. Blood pressure must be measured twice with at least 3 min apart
- Blood draw for hematology (CBC with platelets, WBC with differential), serum chemistry including FPG, and coagulation as detailed in section 6.7.1
- Urinalysis

- Collect plasma sample for drug exposure verification
- Assess adverse events and record concomitant medications

7.2.3 Visit 5 – Procedures (week 6)

- The subject must be queried to assess compliance with a minimum of a 10 h fast prior to blood draw to ensure the FPG values can be accurately determined. Only water is permitted. If a subject has not fasted for 10 h, the subject should return within a week after proper fasting.

- Diary and SMBG review
- Vital Signs: blood pressure, pulse, temperature, respiratory rate taken in the sitting position after at least 5 minutes of rest. Blood pressure must be measured twice with at least 3 min apart
- Dispense study medication
- Blood draw for hematology (CBC with platelets, WBC with differential), serum chemistry including FPG, and coagulation as detailed in section 6.7.1
- Urinalysis
- Collect plasma sample for drug exposure verification
- Assess adverse events and record concomitant medications

7.2.4 Visit 6 – Procedures (week 12)

- The subject must be queried to assess compliance with a minimum of a 10 h fast prior to blood draw to ensure the FPG values can be accurately determined. Only water is permitted. If a subject has not fasted for 10 h, the subject should return within a week after proper fasting.

- Diary and SMBG review
- Diet and exercise counseling
- Physical examination
- Vital Signs: blood pressure, pulse, temperature, respiratory rate taken in the sitting position after at least 5 minutes of rest. Blood pressure must be measured twice with at least 3 min apart
- Dispense study medication
- Blood draw for hematology (CBC with platelets, WBC with differential), serum chemistry including FPG, and coagulation as detailed in section 6.7.1

- Urinalysis
- Collect plasma sample for drug exposure verification
- Assess adverse events and record concomitant medications

7.2.5 Visit 7 – Procedures (week 18)

- The subject must be queried to assess compliance with a minimum of a 10 h fast prior to blood draw to ensure the FPG values can be accurately determined. Only water is permitted. If a subject has not fasted for 10 h, the subject should return within a week after proper fasting.

- Diary and SMBG review
- Vital Signs: blood pressure, pulse, temperature, respiratory rate taken in the sitting position after at least 5 minutes of rest. Blood pressure must be measured twice with at least 3 min apart
- Dispense study medication
- Blood draw for hematology (CBC with platelets, WBC with differential), serum chemistry including FPG, and coagulation as detailed in section 6.7.1
- Urinalysis
- Collect plasma sample for drug exposure verification
- Assess adverse events and record concomitant medications

7.2.6 Visit 8 – Procedures (week 24)

- The subject must be queried to assess compliance with a minimum of a 10 h fast prior to blood draw to ensure the FPG values can be accurately determined. Only water is permitted. If a subject has not fasted for 10 h, the subject should return within a week after proper fasting.

- Diary and SMBG review
- Diet and exercise counseling
- Physical examination
- Vital Signs: blood pressure, pulse, temperature, respiratory rate taken in the sitting position after at least 5 minutes of rest. Blood pressure must be measured twice with at least 3 min apart
- 12 lead ECG taken in the supine position after at least 5 minutes of rest
- Dispense study medication

- Blood draw for hematology (CBC with platelets, WBC with differential), serum chemistry including FPG, and coagulation as detailed in section 6.7.1
- Urinalysis
- Collect plasma sample for drug exposure verification
- Assess adverse events and record concomitant medications

7.3 Extension Phase

7.3.1 Visit 9 – Procedures (week 36)

- The subject must be queried to assess compliance with a minimum of a 10 h fast prior to blood draw to ensure the FPG values can be accurately determined. Only water is permitted. If a subject has not fasted for 10 h, the subject should return within a week after proper fasting.

- Diary and SMBG review
- Vital Signs: blood pressure, pulse, temperature, respiratory rate taken in the sitting position after at least 5 minutes of rest. Blood pressure must be measured twice with at least 3 min apart
- Dispense study medication
- Blood draw for hematology (CBC with platelets, WBC with differential), serum chemistry including FPG, and coagulation as detailed in section 6.7.1
- Urinalysis
- Collect plasma sample for drug exposure verification
- Assess adverse events and record concomitant medications

7.3.2 Visit 10 – Procedures (week 48)

- The subject must be queried to assess compliance with a minimum of a 10 h fast prior to blood draw to ensure the FPG values can be accurately determined. Only water is permitted. If a subject has not fasted for 10 h, the subject should return within a week after proper fasting.

- Diary and SMBG review
- Diet and exercise counseling
- Physical examination

- Vital Signs: blood pressure, pulse, temperature, respiratory rate taken in the sitting position after at least 5 minutes of rest. Blood pressure must be measured twice with at least 3 min apart
- Dispense study medication
- Blood draw for hematology (CBC with platelets, WBC with differential), serum chemistry including FPG, and coagulation as detailed in section 6.7.1
- Urinalysis
- Collect plasma sample for drug exposure verification
- Assess adverse events and record concomitant medications

7.3.3 Visit 11 – Procedures (week 60)

- The subject must be queried to assess compliance with a minimum of a 10 h fast prior to blood draw to ensure the FPG values can be accurately determined. Only water is permitted. If a subject has not fasted for 10 h, the subject should return within a week after proper fasting.

- Diary and SMBG review
- Vital Signs: blood pressure, pulse, temperature, respiratory rate taken in the sitting position after at least 5 minutes of rest. Blood pressure must be measured twice with at least 3 min apart
- 12 lead ECG taken in the supine position after at least 5 minutes of rest
- Dispense study medication
- Blood draw for hematology (CBC with platelets, WBC with differential), serum chemistry including FPG, and coagulation as detailed in section 6.7.1
- Urinalysis
- Collect plasma sample for drug exposure verification
- Assess adverse events and record concomitant medications

7.3.4 Visit 12 – Procedures (week 72)

- The subject must be queried to assess compliance with a minimum of a 10 h fast prior to blood draw to ensure the FPG values can be accurately determined. Only water is permitted. If a subject has not fasted for 10 h, the subject should return within a week after proper fasting.

- Diary and SMBG review
- Diet and exercise counseling
- Physical examination
- Vital Signs: blood pressure, pulse, temperature, respiratory rate taken in the sitting position after at least 5 minutes of rest. Blood pressure must be measured twice with at least 3 min apart
- Dispense study medication
- Blood draw for hematology (CBC with platelets, WBC with differential), serum chemistry including FPG, and coagulation as detailed in section 6.7.1
- Urinalysis
- Collect plasma sample for drug exposure verification
- Assess adverse events and record concomitant medications

7.3.5 Visit 13 – Procedures (week 84)

- The subject must be queried to assess compliance with a minimum of a 10 h fast prior to blood draw to ensure the FPG values can be accurately determined. Only water is permitted. If a subject has not fasted for 10 h, the subject should return within a week after proper fasting.

- Diary and SMBG review
- Vital Signs: blood pressure, pulse, temperature, respiratory rate taken in the sitting position after at least 5 minutes of rest. Blood pressure must be measured twice with at least 3 min apart
- Dispense study medication
- Blood draw for hematology (CBC with platelets, WBC with differential), serum chemistry including FPG, and coagulation as detailed in section 6.7.1
- Urinalysis
- Collect plasma sample for drug exposure verification
- Assess adverse events and record concomitant medications

7.3.6 Visit 14 – Procedures (week 96)

- The subject must be queried to assess compliance with a minimum of a 10 h fast prior to blood draw to ensure the FPG values can be accurately determined. Only water is

permitted. If a subject has not fasted for 10 h, the subject should return within a week after proper fasting.

- Diary and SMBG review
- Physical examination
- Vital Signs: blood pressure, pulse, temperature, respiratory rate taken in the sitting position after at least 5 minutes of rest. Blood pressure must be measured twice with at least 3 min apart
- 12 lead ECG taken in the supine position after at least 5 minutes of rest
- Blood draw for hematology (CBC with platelets, WBC with differential), serum chemistry including FPG, and coagulation as detailed in section 6.7.1
- Urinalysis
- Collect plasma sample for drug exposure verification
- Assess adverse events and record concomitant medications

7.3.7 Visit 15 – Exit Visit (week 97)

Follow-up is planned at approximately one week after the last dose is administered. If subjects have an ongoing adverse event, the subject will be followed until the adverse event is resolved or returns to baseline. All possible attempts will be made to document resolution of acute and chronic toxicities. Diary and SMBG review

- Physical examination
- Vital Signs: blood pressure, pulse, temperature, respiratory rate taken in the sitting position after at least 5 minutes of rest. Blood pressure must be measured twice with at least 3 min apart
- 12 lead ECG taken in the supine position after at least 5 minutes of rest
- Blood draw for hematology (CBC with platelets, WBC with differential), serum chemistry including FPG, and coagulation as detailed in section 6.7.1
- Urinalysis
- Assess adverse events and record concomitant medications

7.4 Early Termination Procedures

Subjects removed from study due to drug related toxicity will be followed until resolution or stabilization of the adverse event. Sponsor must be notified in the event that a subject withdraws or is withdrawn from the study.

Subjects who withdraw consent and have received study drug will have a follow-up examination, including a complete physical examination, vital signs, ECG, CBC, urinalysis, and serum chemistry tests.

8 QUALITY CONTROL AND ASSURANCE

The clinical research facility will be monitored by the study monitor to ensure correct performance of the study procedures and assure that the study will be conducted according to the protocol and relevant regulatory requirements. CRF entries will be verified with the source documentation.

Quality control principles will be applied throughout the performance of this study by following the SOPs of the CRO and the sponsor. Review procedures will be implemented at the CRO for all documents that are generated in relation to the study.

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

The primary objective of this trial is to assess the efficacy of EGT0001442 in treatment-naïve type-2 diabetic patients or patients on a single oral anti-diabetic drug in combination with diet and exercise with an HbA1c between 7 and 10%. Efficacy, in this case, is defined as a significant reduction in HbA1c at week 24 when compared to placebo. The effect of EGT0001442 on fasting glucose, blood pressure, body weight and the general safety of EGT0001442 in patients with T2DM will also be explored.

Statistical analyses and summaries of safety and tolerability will be performed using SAS® software (SAS Institute, Cary, NC). In all cases, significance will be judged at the α=0.05 level. No multiplicity adjustment will be required for the single primary endpoint.

9.1.1 Handling Dropouts, Multiples, Missing Data, and Outliers

Discontinuation criteria are explained in Section 6.11. Patients who discontinue will not be replaced. Data will be evaluated for any bias in the pattern of missing data prior to inference testing. Absence of a discernable pattern will be taken as a reliable indication that the incidences of missing data are random occurrences and will not be addressed further. Clinically relevant patterns of missing data will be summarized in the Clinical Trial Report and summarized as notes to any affected tables and listings. Missing data will not be imputed and the observation for that subject will be effectively deleted for that subject.

9.1.2 Multiple Comparisons / Multiplicity

There is a single primary endpoint in this study and no correction for multiple comparisons is needed. Important secondary endpoints are considered exploratory and will not be corrected.

9.2 Determination of Sample Size

Approximately 300 patients will be enrolled and equitably allocated to receive either 20 mg/day EGT0001442 or placebo.

The sample size of 150 subjects per group was calculated based on the following assumptions:

1. This effect size is the mean difference between baseline and week 24. The active doses will decrease the HbA1c by 0.4%.
2. The placebo will not experience a substantive average decrease in mean HbA1c from baseline to week 24
3. The standard deviation of this difference is the same for both groups and is 1.0%.
4. The study design is balanced and the two-sided significance level for the hypothesis is 0.05.

Under the above assumptions, an evaluable sample size of 131 evaluable patients per treatment arm yields approximately 90% power that EGT0001442 treatment will be found to be significantly different from placebo. A sample size of 150 subjects per treatment arm will be enrolled to account for any subject lost-to-follow-up.

9.3 Analysis Populations

This study will be conducted at multiple investigative sites and will likely involve variable numbers of subjects at each site. Enrollment will be on a competitive basis but will be capped at 90 subjects in one center.

All patients in the Intent-to-Treatment (ITT) sample will be analyzed according to the treatment they were randomized to receive, and not according to what they actually received, if different. All efficacy analyses will be performed on the ITT sample. All patients in the Per Protocol (PP) sample will be analyzed according to the treatment actually received, and not according to the treatment they were randomized to receive, in the event there is a discrepancy. The analyses of primary efficacy endpoint and selected secondary efficacy endpoints will be performed on the PP sample. The Safety sample will include all randomized patients who have received study drug. The safety sample will be used for safety analysis.

9.4 Demographics and Baseline Characteristics

Patients must meet all inclusion criteria and none of the exclusion criteria in order to participate in the study. Demographic characteristics include age, gender, race, ethnicity, and study center. Baseline characteristics include baseline HbA1c values, blood pressure, Body Mass Index (BMI in kg/m^2), whether treatment naïve or not. Summary descriptive statistics will include counts and percentages for discrete variables and estimation of means, standard deviations, medians, inter-quartile range, minimum and maximum for continuous metrics.

9.5 Analysis of Efficacy

Efficacy data includes HbA1c, FPG, body weight, systolic and diastolic blood pressure, and % of subject who achieve HbA1c <7% at week 24. Observed data will be summarized as counts and percentages for discrete variables and estimation of means, standard deviations, medians, inter-quartile range, minimum and maximum for continuous metrics. All data will be presented in by-subject listings and included in the clinical trial report.

9.5.1 Primary Efficacy Endpoint

The primary hypothesis is that EGT0001442 reduces HbA1c after 24 weeks of treatment when compared to placebo controls. Change in HbA1c will be estimated as HbA1c at 24 weeks minus HbA1c at baseline. The two groups will be compared with a t-test at a significance level of 0.05. For subjects that receive rescue medication due to hyperglycemia, the last HbA1c prior to receiving rescue medication will be carried forward to week 24.

9.5.2 Secondary Efficacy Endpoints

The secondary endpoints are considered exploratory and will not be corrected for multiplicity. The first secondary hypothesis is that EGT0001442 reduces FPG at weeks 2 and 24 when compared to controls. Change in FPG for each follow up visit will be estimated as follow-up minus baseline and the two treatment groups will be compared with two paired t-tests.

The second hypothesis is that EGT0001442 reduces the HbA1c to less that 7% of more patients when compared to placebo. HbA1c categories will be assessed for each patient as $<7\%$ or $\geq 7\%$ of each subject. The 2x2 contingency table of treatment by HbA1c category will be analyzed with a χ^2 test.

The third hypothesis is that EGT0001442 reduces blood pressure compared to placebo. Systolic and Diastolic blood pressure will be measured at baseline and at weeks 2 and weeks 24. Change in each blood pressure metric for both follow up visits will be estimated as follow-up minus baseline and the two treatment groups will be compared with four paired t-tests.

The fourth hypothesis is that EGT0001442 reduces body weight compared to placebo. Body weight will be measured at baseline and at weeks 2 and weeks 24. Change in body weight for both follow up visits will be estimated as follow-up minus baseline and the two treatment groups will be compared with two paired t-tests.

The final secondary hypothesis is that EGT0001442 induced change in HbA1c is evident over time, present at week 24 and maintained over the 96 weeks of the study. HbA1c is collected at baseline and weeks 2, 6, 12, 24, 36, 48, 60, 72, 84 and 96. Repeated measures of HbA1c will be analyzed with a linear mixed effect model to assess the overall treatment effect. Subsequently the change in each time point will be estimated as described for the primary endpoint and evaluated with 10 t-tests.

9.5.3 Additional Efficacy Endpoints

As with HbA1c, repeated measures are available for body weight, systolic and diastolic blood pressure, and fasting plasma glucose. Repeated measures of these variables will be analyzed individually with a linear mixed effect model to assess the overall treatment effect. Subsequently the change in each time point will be estimated as described for the primary endpoint and evaluated with t-tests.

The effect of demographic covariates such as gender, race, age, treatment center, will be evaluated on the primary endpoint and selected secondary endpoints (FPG, blood pressure, and body weight) using Analysis of Covariance. Demographic variables will be included in the model of change in the dependent variable with treatment.

9.6 Analysis of Safety

Safety data includes adverse events (AEs), physical exam results, vital signs, ECG results, and clinical lab results including serum chemistry, hematology, and urinalysis. Observed data will be described as counts and percentages for discrete variables and estimation of means, standard deviations, medians, inter-quartile range, minimum and maximum for continuous metrics. All patients will be included in the safety analysis. All safety data will be presented in by-subject listings and included in the clinical trial report.

9.6.1 Adverse Events

Adverse events will be mapped to preferred term and body system using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. The number and percentage of patients reporting adverse events will be determined by relationship to treatment and by severity of the event. Drug-related adverse events will be considered those to be at least possibly related to EGT0001442 administration.

Adverse event listings will be provided for the following subsets:

- All treatment emergent AEs (TEAEs)
- All TEAEs at least possibly related to EGT0001442
- Serious TEAEs (if any)
- TEAEs leading to study discontinuation (if any)

AEs are treatment emergent if occurring on or after EGT0001442 administration. TEAEs will be considered at least possibly related to EGT0001442 based on the investigators assessment. Only TEAEs will be tabulated in summary tables.

Tabulations will display TEAEs by severity, and relationship to EGT0001442.

9.6.2 Adverse event of special interest

9.6.2.1 Genitourinary infections

Genitourinary infections as defined in Section 6.9.7.1 will be summarized. Event terms, signs, symptoms, infectious agent (bacterial or fungal), and treatment undertaken will be documented in the listing.

9.6.2.2 Major Adverse Cardiovascular Event (MACE)

All events that potentially represent myocardial infarction, cerebrovascular accident (stroke), acute coronary syndrome, or cardiovascular death are to be evaluated by an independent adjudication committee. There will not be any analysis performed.

9.6.2.3 Hypoglycemia

Severe hypoglycemia as defined in Section 6.9.7.3 will be presented in a listing and summarized.

9.6.2.4 Renal and Urinary disorders

Events as defined in Section 6.9.7.1 will be summarized. Event terms, signs, and symptoms will be documented in the listing.

9.6.3 Clinical and Laboratory Events and Analyses

Clinical and laboratory metrics are measured at baseline and weeks 2, 6, 12 and 24 during the study. During the treatment extension they are measured every 12 weeks up to a total of 96 weeks. These variables include vital signs (blood pressure, respiration, and temperature), Clinical laboratory (see section 6.7 for a complete list) and ECGs.

Laboratory data will be summarized using Low-Normal-High shift tables. ECG results will be summarized as changes from baseline in intervals. Abnormalities as well as changes from previous assessment will be listed.

9.6.4 Concomitant Medications

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODRUG). A by-subject listing of concomitant medications will include all medications taken during the study. All medications started prior to the administration of the study drug will be included in the data but will be flagged as prior. Only the concomitant medication use will be summarized.

9.7 Interim Analysis

An independent Data and Safety Monitoring Board (DSMB) will monitor the safety of this study. The objectives of the DSMB are to assess drug safety and allow for protocol modification or early stopping due to safety concerns. The DSMB members will include at least one statistician, one clinician of relevant specialty, and one endocrinologist that is familiar with the care of patients with type 2 diabetes. No interim efficacy assessment will be performed.

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Investigators and Study Administrative Structure

Information regarding key personnel involved in the conduct of the study, including names and contact details of participating investigators, monitors, clinical laboratories, technical departments and/or institutions, as well as information on members of additional study committees, will be found in the study files of the study sites.

10.2 Institutional Review Board (IRB) or Independent Ethics Committee (IEC) Approval

This protocol, informed consent document, relevant supporting information, and all types of subject recruitment or advertisement information must be submitted to the IEC or IRB for review and must be approved by The Sponsor and the IEC/IRB before the study is initiated. Any amendments or addenda to the protocol must also be approved by the IEC/IRB prior to implementing changes in the study. The Investigator is responsible for keeping the IEC/IRB apprised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case at least once a year. The Investigator must also keep the IEC/IRB informed of any SAEs occurring to subjects under their supervision.

10.3 Ethical Conduct of the Study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by Good Clinical Practice Guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s). This may include an inspection by the sponsor representatives and/or their designee and/or FDA representatives at any time. The investigator must agree to the inspection of study-related records by the FDA/sponsor representatives, and must allow direct access to source documents to the FDA/sponsor representatives.

The investigator is responsible for complying with the protocol and all appropriate regulations and guidelines governing global clinical research. Additionally, he/she is responsible for ensuring that all participating staff members are adequately trained and competent to perform his/her assigned tasks.

Modifications to the study protocol will not be implemented by either the sponsor or the investigator without agreement by both parties. However, the investigator may implement a deviation form, or a change of, the protocol to eliminate an immediate hazard(s) to the trial subjects without prior IRB/sponsor approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the IRB/sponsor.

Any deviations from the protocol must be fully explained and documented by the investigator. The circumstances, action taken and impact of the deviation on the trial must be

communicated by the Principal Investigator to the designated Medical Monitor. Any subsequent actions will be assessed by the designated Medical Monitor and documented.

10.4 Patient Information and Consent

Prior to the beginning of the study, the investigator must have the EC/IRB written approval/ favorable opinion of the written Informed Consent Form and any other written information to be provided to subjects. The written approval of the EC/IRB together with the approved subject information/Informed Consent Forms must be filed in the study files. The Informed Consent Form must contain all elements required by the FDA under 21 CFR Part 50 and the International Conference on Harmonisation (ICH) Good Clinical Practices (GCP) Guidelines (E6) in addition to any other elements required by state, local or institutional policy.

Written informed consent must be obtained before any study specific procedure takes place. Participation in the study and date of informed consent given by the subject should be documented appropriately in the subject's files. A copy of the signed informed consent form must be provided to the subject. If applicable, it will be provided in a certified translation in the language understood by the subject if not English. Signed consent forms must remain in each subject's study file and must be available for verification by study monitors at any time.

10.5 Patient Confidentiality

The information obtained during the conduct of this clinical study is confidential, and disclosure to third parties other than those noted below is prohibited. Information obtained during the conduct of this study will be used by The Sponsor in connection with the development of the study drug. The study Investigator is obliged to provide the Sponsor with complete test results and all data developed in this study. Subject-specific information may be provided to other appropriate medical personnel only with the subject's permission. To ensure compliance with current ICH guidelines, data generated by this study must be available for inspection upon request by representatives of national and local health authorities, the Sponsor and the IRB for each study site.

Subject names and other identifiers, such as photographs, audio or videotapes, may not be disclosed in any publication without prior written authorization from the subject.

10.6 Study Monitoring

An authorized Sponsor representative will conduct site visits to inspect study data, subjects' medical records and CRFs in accordance with ICH guidelines, GCPs and the respective local and national government regulations and guidelines.

The Investigator will permit authorized representatives of the Sponsor and the respective national or local health authorities to inspect facilities and records relevant to this study.

10.7 Case Report Forms and Study Records

For each subject consented, a case report form (CRF) will be supplied and maintained by the CRO staff and signed by the investigator or authorized designee to indicate that he/she has reviewed and agrees with the entered data. This also applies to those subjects who fail to complete the trial. The reason a subject is withdrawn must be recorded in the case report form.

Entries made in the CRF must be verifiable against source documents. Source documents are defined as all medical records, medical notes, laboratory results, ECG traces and any additional document other than the CRF that has original subject information contained within it. The diary card that subjects will complete with meal information will be archived but meal information will not be entered in the database. Whether the subject was fasting for 10 hr or not prior to sample collection will be captured in the CRF.

All CRFs and source documents should be completed following GCPs and the CRO's standard operating procedures.

10.8 Protocol Violations/Deviations

Protocol "violations" include deviations from the inclusion and exclusion criteria, concomitant medication restrictions, and any other protocol requirement that results in a significant added risk to the patient or has an impact on the quality of the data collected or the outcome of the study. Protocol violations must be reported to the Ethics Committee or Institutional Review Board in a timely manner. Protocol violations must be reported in the final study report.

A protocol deviation occurs when there is non-adherence to study procedures or schedules, as specified by the protocol, which does not involve inclusion/exclusion criteria or the primary endpoint and which does not place the patient at any added risk or affect the data quality or study outcome. If deviations occur, such as a missed visit or missed sampling window, the investigator must decide whether to proceed, for example, whether or not to complete the visit or sample collection outside of the protocol-defined window. The sponsor's medical monitor must be notified immediately when protocol deviations are discovered so that a decision can be made about the continued participation of the subject in the study.

A departure from the protocol for an individual subject can only be made without the Sponsor approval in the event of an emergency. The nature and reasons for the protocol deviation will be recorded in the CRF and the Principal Investigator must notify the Sponsor.

10.9 Access to Source Documentation

Authorized Sponsor representatives will conduct site visits to inspect study data, subject medical records and CRFs in accordance with ICH guidelines, GCP and the respective local and national government regulations and guidelines.

The Investigator will permit authorized representatives of the Sponsor and the respective national or local health authorities to inspect facilities and records relevant to this study.

Each center will be visited at regular intervals by a monitor to ensure compliance with the study protocol, GCP and legal aspects. This will include on-site checking of the case report forms (CRF) for completeness and clarity, cross-checking with source documents, and clarification of administrative matters.

All CRF data will be entered into a clinical database. Following the correction of any errors, the clinical database will be locked.

10.10 Data Generation and Analysis

For each subject who is randomized to receive study drug, a case report form (CRF) must be maintained by a trial coordinator and signed by the investigator or authorized designee to indicate that he/she has reviewed and agrees with the entered data. This also applies to those subjects who fail to complete the trial. The reason a subject is withdrawn must be recorded in the CRF. Subjects whose eligibility is not confirmed on day 1 are considered screen failure and no CRF will be maintained for those subjects.

Entries made in the CRF must be either verifiable against source documents, or have been directly entered into the CRF, in which case the entry in the CRF will be considered as the source data. Source documents are defined as all medical records, medical notes, laboratory results, ECG traces and any additional document other than the CRF that has original patient information contained within it.

All source documents must be legible. Errors must be lined out and the correction must be made, initialed and dated by the person making the correction.

The Sponsor or designated CRO is responsible for data processing and data query. The investigator or designated staff is responsible for query resolution and data clarification.

10.11 Retention of Data

The study file and all source data should be retained until notification given by the sponsor for destruction. If the investigator withdraws from the trial and relinquishes his/her responsibility for the maintenance and retention of records, he/she must notify the Sponsor in writing so arrangements can be made to properly store the trial materials.

10.12 Publication and Disclosure Policy

All data and results and all intellectual property rights in the data and results derived from the study will be the property of the Sponsor, who may utilize the data in various ways, such as for submission to government regulatory authorities or disclosure to other investigators.

No publication or disclosure of study results will be permitted except as specified in a separate, written agreement between Theracos, Inc. and the investigator. If results of this study are reported in medical journals or at meetings, all subjects' identities will remain confidential.

11 REFERENCE LIST

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Appendix 1 Schedule of Events

	Screening & Run-in		Primary Efficacy Phase						Extension Phase						
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**ET**
Time Relative to Randomization Visit (weeks)[1]	**-5**	**-2**	**0**	**2**	**6**	**12**	**18**	**24**	**36**	**48**	**60**	**72**	**84**	**96**	
Informed Consent	X														
Screening for I/E criteria	X	X	X												
Medical History	X														
Diet & exercise counseling		X				X		X		X		X			
Diary Review			X	X	X	X	X	X	X	X	X	X	X	X	X
Discontinue anti-diabetic medication		X													
Randomization			X												
Physical exam	X					X		X		X		X		X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X		X					X			X			X	X
Dispense study medication		X	X		X	X	X	X	X	X	X	X	X		
Blood draw for clinical lab test[2]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
PK sample				X	X	X	X	X	X	X	X	X	X	X	
Urinalysis[3]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
AE[4]			X	X	X	X	X	X	X	X	X	X	X	X	X
Con Med			X	X	X	X	X	X	X	X	X	X	X	X	X

[1] Screening period may last up to 21 days (V1 to V2), Run-in period is to be 14±3 days (V2 to V3), V3 to V4 window is 14±3 days, all other visit windows are the nominal duration from randomization ± 7 days.

[2] Blood sample for these lab tests at the designated visit:

V1: CBC, electrolytes, BUN, creatinine, Lipids (TG, TC, HDL-C), ALT, AST, bilirubin (total and direct), PT, HbA1c, FPG, TSH, aPTT, Hepatitis Screen (HBsAg, HBcAg, HCV)

V3: CBC, electrolytes, BUN, creatinine, Lipids (TG, TC, HDL-c), ALT, AST, bilirubin (total and direct), HbA1c, FPG

V4: CBC, electrolytes, BUN, creatinine, HbA1c, FPG

V5: CBC, electrolytes, BUN, creatinine, HbA1c, FPG

V6: CBC, electrolytes, BUN, creatinine, Lipids (TG, TC, HDL-c), ALT, AST, bilirubin (total and direct), HbA1c, FPG

V7: CBC, electrolytes, BUN, creatinine, HbA1c, FPG

V8-V14 and ET: CBC, electrolytes, BUN, creatinine, Lipids (TG, TC, HDL-c), ALT, AST, bilirubin (total and direct), HbA1c, FPG

[3] Clean catch sample to be collected at each visit. If urine is dipstick positive for WBC or blood sample is to be sent for microscopic evaluation and culture. Urine pregnancy test and drug screen on screening (visit 1)

[4] Adverse events of special interest are specified to be:

- Cardio- and cerebro- vascular events,
- Genitourinary infections
- Increase in creatinine from baseline by 0.5 mg/dL or more
- Increase in ALT, AST or bilirubin to >3x ULRR

Appendix 2 Estimating glomerular filtration rate

Estimating the glomerular filtration rate (eGFR), as calculated by the modification of diet in renal disease study equation (MDRD), should be calculated based on following equation:

GFR (mL/min/1.73 m^2) = **175** x $(S_{cr})^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if female) x (1.212 if African American) (conventional units)

Appendix 3 Sponsor Signatures

Study Title: Efficacy and safety of EGT0001442 compared with placebo in patients with type 2 diabetes mellitus inadequately controlled by diet and exercise and up to one oral anti-diabetes agent.

Study Number: THR-1442-C-418

Final Date: 02 February 2011

This clinical study protocol was subject to critical review and has been approved by the sponsor. The following personnel contributed to writing and/or approving this protocol:

Signed:_____ Date:_____
Yuan-Di Halvorsen, Ph.D.
Protocol Originator
Consultant for Theracos, Inc.

Signed:_____ Date:_____
R. Paul Aftring, M.D., Ph.D.
Medical Director
Consultant for Theracos, Inc.

Signed:_____ Date:_____
Ulrich Granzer, Ph.D.
Regulatory Affairs
Consultant for Theracos Inc.

Appendix 4 Investigator's Signature

Study Title: Efficacy and safety of EGT0001442 compared with placebo in patients with type 2 diabetes mellitus inadequately controlled by diet and exercise and up to one oral anti-diabetes agent.

Study Number: THR-1442-C-418

Final Date: 02 February 2011

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Signed:_____ Date:_____
Principal Investigator