X-82 to treat Age-related Macular Degeneration

PROTOCOL X82-OPH-201

A Randomized, Double-Masked, Placebo-Controlled, Dose-Finding, Non-Inferiority Study of X-82 plus *prn* ivt anti-VEGF compared to *prn* ivt anti-VEGF monotherapy in neovascular AMD

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TYROGENEX, INC.

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Rockville, MD 20850

PROTOCOL SUMMARY

Protocol Number	X82-OPH-201
Title	A randomized, double-masked, placebo-controlled, dose-finding, non-inferiority study of X-82 plus *prn* ivt anti-VEGF compared to *prn* ivt anti-VEGF monotherapy in neovascular AMD
Sponsor	Tyrogenex, Inc.
Regulatory Status	Phase 2b
Objectives	The objective is to evaluate the safety and efficacy of X-82 at three doses as determined by a comparison of the mean visual acuity at 52 weeks in subjects with neovascular AMD
Study Design	Double-masked, placebo-controlled multicenter clinical trial in which subjects will be randomized (1:1:1:1) with one of three doses of X-82 plus ivt anti-VEGF *prn* versus placebo plus ivt anti-VEGF *prn*.
Study Population	Subjects with neovascular AMD
Number of Subjects	Approximately 132 subjects
Number of Groups/Arms	At least 132 subjects will be randomized to 50, 100 or 200 mg X-82 versus placebo in a 1:1:1:1 ratio (33:33:33:33 subjects).
Gender/Age	Males and females, 50 years of age or older
Number & location of Centers	35 to 45 sites in the USA
Key Eligibility Criteria	Males and females, aged 50 years or older with wet AMD diagnosed for at least 6 months and receiving ivt anti-VEGF at least every 8 weeks for the past two injections and have demonstrated a reduction in macular fluid or macular thickness compared to the OCT prior to the last anti-VEGF injection at Day -29. BCVA must be 20/320 (25 letters) or better in both eyes. Subjects may not have undergone any intraocular surgery of the study eye within 6 months of screening. Previous posterior vitrectomy of the study eye is not allowed within 30 days of Screening Visit 1
Investigational Product	Multiples of 50 mg and 100 mg X-82 tablets or matching placebo tablets administered per os (po) once a day (qd).
Study Procedures	Subjects will be screened for inclusion into the study after providing written informed consent between Day -29 and Day -1. Screening procedures to be performed between Day -14 and Day -1 will include ECG, laboratory analyses, BCVA, ophthalmological examination, IOP, FA, fundus photography and SD-OCT and subjects will need to demonstrate a reduction in macular fluid or macular thickness after receiving an injection of anti-VEGF at Day -29. On Day -1 (28 days after the initial anti-VEGF injection) subjects will receive a further injection of anti-VEGF and then be dispensed with study medication to be commenced the following day, and which will be taken with food at the same time each day for the duration of the study. Subjects will return for study assessments every 4 weeks until week 52. Follow-up assessments will occur at week 56. Subjects will be assessed for the need for retreatment with anti-VEGF therapy based on specific retreatment criteria.

Clinical Parameters	The following clinical parameters will be evaluated: Slit lamp examination Fundus examination Intraocular pressure Best corrected visual acuity (ETDRS) Fluorescein angiography/fundus photography Spectral Domain Optical coherence tomography
Safety Assessments	Systemic and ocular safety will be evaluated by assessing: ECG Laboratory analyses Adverse events (AEs) Serious adverse events (SAEs)
Efficacy Outcomes	**Primary efficacy measure:** The mean change in ETDRS visual acuity score at week 52 **Secondary efficacy measures**: The mean number of anti-VEGF injections at week 52 Change in OCT parameters from Day -1 to week 52 Change in FA parameters from Day -1 to week 52 Time from Day 1 to first anti-VEGF injection
Interim analyses	One interim analysis will be performed to enable the DSMB of the trial to perform a full benefit/risk assessment and recommend a course of action to Sponsor. A second interim analysis will be performed to enable the DSMB and a small group of individuals designated by the Sponsor to plan future trials of X82 in wet AMD or other indications.

1 INVESTIGATOR SIGNATURE PAGE

A randomized, double-masked, placebo-controlled, dose-finding, non-inferiority study of X-82 plus *prn* ivt anti-VEGF compared to *prn* ivt anti-VEGF monotherapy in neovascular AMD.

My signature confirms that I have carefully read, and that I understand this protocol. I agree to follow the study procedures as outlined in this protocol in compliance with Good Clinical Practice and all other regulatory requirements.

This protocol contains confidential information with respect to products and clinical trials. I agree to hold this information in confidence and not to disclose it to any third parties until this information becomes a matter of public knowledge, or until a formal agreement for that purpose has been entered into by the parties.

_____

Print Name of Investigator

_____ _____

Investigator's Signature Date

2 TYROGENEX SIGNATURE PAGE

TITLE: A randomized, double-masked, placebo-controlled, dose-finding, non-inferiority study of X-82 plus *prn* ivt anti-VEGF compared to *prn* ivt anti-VEGF monotherapy in neovascular AMD

Protocol Author: Daniel E. Salazar, Ph.D.

Date: Signature:_____

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ABBREVIATIONS

AE	Adverse event
ALT (SGPT)	Alanine aminotransferase
ALP	Alkaline phosphatase
AMD	Age-related macular degeneration
ANC	Absolute neutrophil count
AREDS	Age-Related Eye Disease Study
AST (SGOT)	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the plasma-concentration time curve
AUC_{0-t}	Area under the plasma-concentration time curve from zero up to the last measureable concentration
AUC_{0-24}	Area under the plasma-concentration time curve from time zero to 24 hours
BCVA	Best corrected visual acuity
BPM	Beats per minute
BSA	Body surface area
BUN	Blood urea nitrogen
CBC	Complete blood count
CHF	Congestive heart failure
C-Kit	CD117 cytokine receptor
C_{max}	Peak drug concentration
CMP	Comprehensive metabolic profile
CNV	Choroidal Neovascularization
CRF	Case Report Form
CRT	Central retinal thickness
CSF	Colony-stimulating factor
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DARC	Digital Angiographic Reading Center
DLT	Dose Limiting Toxicity
ETDRS	Early Treatment Diabetic Retinopathy Study
ECHO	Echocardiogram
FA	Fluorescein angiography
FDA	Food and Drug Administration
GIST	Gastrointestinal stromal tumor
HIPAA	Health Insurance Portability and Accountability Act
HNSTD	Highest non-severely toxic dose

ICF	Informed Consent Form
IB	Investigator's Brochure
IRC	Independent Reading Center
INR	International normalized ratio
IOP	Intraocular pressure
IRB	Institutional Review Board
IVT	Intravitreal
MI	Myocardial infarction
MTD	Maximum tolerated dose
N/A	Not applicable
NCI	National Cancer Institute
NOAEL	No observed adverse effect level
NYHA	New York Heart Association
PDGF	Platelet derived growth factor
PDGFR	Platelet derived growth factor receptor
PDT	Photodynamic therapy
PG	Pharmacogenetic
PHI	Protected health information
PK	Pharmacokinetic
PO	Per os, orally
PR	Progesterone receptor
PR+	Progesterone receptor positive
PVC	Polyvinyl chloride
QA	Quality assurance
QTcF	QT interval corrected for heart rate using the Fridericia method of correction
RAP	Retinal angiomatous proliferation
RPE	Retinal pigment epithelium
RET	RET onco-gene "Rearranged during transfection"
RTK	Receptor tyrosine kinases
SAE	Serious adverse event
SD-OCT	Spectral Domain Optical coherence tomography
STD_{10}	Severely toxic dose in 10% of animals
$T_{1/2}$	Terminal half-life
TKI	Tyrosine kinase inhibitor
TTP	Time to tumor progression
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor

3 INTRODUCTION

3.1 AGE-RELATED MACULAR DEGENERATION (AMD)

Age-related macular degeneration (AMD) is one of the most common causes of vision loss among adults in the United States of America (USA) and other developed countries. Late AMD is classified into two forms; the atrophic or "dry" form and the exudative, neovascular or wet form. Although only about 10% of people with AMD will develop the neovascular form of the disease, neovascular AMD (nAMD) accounts for 90% of the blindness associated with AMD [1].

In nAMD, severe vision loss is caused by abnormal blood vessels that invade the macula, the region providing sharp resolution and central vision. Leakage from these vessels, as well as the vessels themselves, causes progressive deterioration in central vision. In functional terms, people with nAMD are unable to read, recognize faces or drive, and the disease often leads to legal blindness. The onset of severe visual changes in nAMD can occur suddenly. Neovascular AMD progresses much more quickly than dry AMD. Within the nAMD category, classic choroidal neovascularization (CNV), in the center of the fovea, is largely responsible for vision loss occurring in a matter of weeks. While occult CNV may progress very slowly, 70% of individuals with untreated subfoveal CNV became legally blind (20/200) within nine months of diagnosis [2].

There are approximately 1.75 million people in the USA with impaired vision resulting from AMD, a number that is expected to triple by the year 2030 as the population ages [3].

3.2 CLINICAL PATHOLOGY

The clinical and histopathological features of AMD include a relationship with age, and the presence of pigmentary disturbances, drusen, thickening of Bruch's membrane which is the innermost layer of the choroid, and basal laminar deposits. Age-related macular degeneration is an advanced stage of a deteriorative process that takes place in all eyes. The primary lesion in AMD appears to reside in the retinal pigment epithelium (RPE), possibly resulting from its high rate of molecular degradation. Beginning early in life, and continuing throughout the life span, cells of the RPE gradually accumulate sacs of molecular debris. These residual bodies (lipofuscin) are remnants of the incomplete degradation of abnormal molecules which have been damaged within the RPE cells or derived from phagocytosed rod and cone membranes. Progressive engorgement of RPE cells with these functionless residues is associated with the extrusion of aberrant materials which accumulate in Bruch's membrane and aggregate in the form of drusen and basal laminar deposits. These excretions contribute to the further deterioration of the RPE. Loss of vision results from death of visual cells due to degeneration of RPE cells, or the effects of leakage from neovascular membranes that invade the region of abnormal extracellular deposits [4]. In particular, when lesions invade the macula and the fovea centralis, central visual loss occurs which impairs facial recognition and the ability to read and to drive a vehicle.

3.3 PHARMACOLOGIC TREATMENT OF NEOVASCULAR AMD

3.3.1 Anti-VEGF Therapy

A significant proportion of subjects diagnosed with the neovascular form of AMD can be treated with drugs that target abnormally high levels of the specific angiogenic growth factor vascular endothelial growth factor (VEGF). VEGF is up-regulated in eyes with neovascular AMD, and promotes the growth of abnormal blood vessels, as well as causing these to leak plasma into the back of the eye resulting in significantly reduced visual acuity over time. Ranibizumab (Lucentis; Genentech) and bevacizumab (Avastin; Genentech) have been designed to block all isoforms of VEGF. Most recently, aflibercept (Eylea; Regeneron Pharmaceuticals) was approved for intravitreal injection in subjects with nAMD; aflibercept binds VEGF-A and PIGF (placental growth factor) to inhibit the binding and activation of these VEGF receptors.

These anti-VEGF therapies have been efficacious for many subjects, particularly in the initial phases of treatment, but require intravitreal injections at monthly or six-weekly intervals. It is now established that a failure to maintain 'knock-down' of the neovascular process, following initial aggressive anti-VEGF therapy, results in the reappearance of the disease pathophysiology within a few months after cessation of anti-VEGF therapy necessitating frequent costly intravitreal treatment to affected eyes. Furthermore, these monthly intravitreal injections are associated with risks of endophthalmitis, retinal detachment, intraocular hemorrhage, increased intraocular pressure and even anaphylaxis. Thus, there is a need for a product which can prevent, or, attenuate the requirement for further anti-VEGF therapy once the pathophysiology has been initially arrested by anti-VEGF therapy or, replace this approach with a longer lasting treatment.

3.3.2 Platelet-Derived Growth Factor (PDGF)

There is growing evidence that the pathophysiology of nAMD involves multiple growth factors beyond VEGF, and there is likely a clinical benefit to targeting multiple pathways simultaneously. The development and propagation of neovascularization involves pro-angiogenic factors, vascular permeability molecules, and inflammatory proteins. While targeting a specific pathophysiologic mechanism, such as VEGF, is effective in halting vascular leakage, it has shown to be only a temporizing treatment. Further benefit may be realized if several components of the cascade are treated simultaneously [13,14].

Platelet-derived growth factor (PDGF) is a growth factor implicated in angiogenesis and formation of nAMD. In contrast to VEGF, which acts on the endothelial cells that line capillaries, PDGF targets the perivascular cells that form the "backbone" of the capillary. Thus targeting VEGF and PDGF simultaneously has been shown to be synergistic for inhibiting blood vessel growth in tumors [15] and in animal models of nAMD [16,17]. As such, clinical studies are underway with other treatment regimens that inhibit both VEGF and PDGF simultaneously [18,19].

Systemic toxicities associated with early generation VEGFR/PDGFR inhibitors have precluded long-term use of these agents in ophthalmology [20]. The advent of newer generation VEGFR/PDGFR inhibitors with improved therapeutic indices may offer a therapeutic alternative for neovascular AMD therapy that would enable delivery of a potent anti-angiogenic agent via the oral route.

3.4 X-82 - A LOW-TOXICITY VEGFR/PDGFR INHIBITOR

X-82 is an oral multi-kinase VEGFR/ PDGFR inhibitor intended for the treatment of pathologic angiogenesis in diseases such as nAMD, von Hippel-Lindau disease and solid tumors. The growth factors VEGF and PDGF are both implicated in the pathogenesis of nAMD, and there is growing evidence that combined inhibition of VEGF and PDGF has a synergistic effect for treatment of nAMD.

Mechanistically, binding of X-82 to its target receptors, i.e., VEGFR and PDGFR, results in inhibition of angiogenesis. X-82 is structurally related to an earlier multi-kinase inhibitor sunitinib and has been designed to improve upon the safety profile without compromising the efficacy of sunitinib. In a diverse panel of human tumor nude mouse xenograft models X-82 displayed comparable activity to sunitinib with respect to tumor growth inhibition. Models of renal cell, colon, pancreatic, melanoma, and leukemia were studied. In these studies the minimum effective dose that gave at least 50% inhibition of tumor growth in a sensitive model was 40 mg/kg twice a day (BID). X-82 has also been tested in a rat model of choroidal neovascularization (CNV), and it was observed to inhibit CNV at both dose levels tested.

Based on the toxicology studies, with an STD_{10} in the rat of 20 mg/kg (120 mg/m^2) daily, 20 mg (capsule formulation) was selected as the starting dose for the first-in-human clinical trial of X-82. The initial clinical evaluation of X-82 is being conducted under IND 108,192, in subjects with solid tumors (Protocol X82-CLI-101). To date, 16 subjects treated at doses ranging from 20 to 400 mg qd and 140 to 200 mg BID (capsule formulation). Subsequently a tablet formulation was developed and 36 subjects have been treated at doses ranging from 50 to 800 mg qd. Among the total of 52 subjects treated to date, X-82 has been well tolerated, with generally mild adverse events reported. A maximum tolerated dose has not yet been reached in this ongoing study. There is an apparent saturation in absorption of the drug at doses close to 400 mg qd. The same tablet formulation has been evaluated in the Phase 1 protocol for AMD (Protocol X82-OPH-102) and will also be used in the phase 2 protocol.

This Phase 2 clinical protocol is designed to evaluate the safety and provide preliminary evidence of efficacy of X-82 tablets for the treatment of choroidal neovascularization secondary to AMD.

3.4.1 Non-Clinical Studies of X-82

3.4.1.1 Toxicology

To assess the safety of X-82, a single escalating dose study was conducted in dogs followed by a seven day repeated dose phase, a 28-day dose range-finding study was conducted in rats, and 28-day repeated dose toxicity studies in rats and dogs were conducted. In the toxicology studies, X-82 was administered orally in order to mimic the planned mode of clinical administration.

In the 28-day repeat-dose toxicity study in the rat, the STD_{10} was determined to be 20 mg/kg/day, the lowest dose tested. Effects seen at this dose included slightly reduced weight gain (2% to 6%), slight reduction in red cells (3% to 15%), elevated ALT and AST (20-100% above control; return to normal at end of recovery period), and mild adrenal vacuolation (males only) and adrenal hypertrophy (females only) which was designated by the pathologist as a non-adverse finding. Hypertrophy of the bone cartilage and growth plate was seen in females only.

Other changes at this dose were typical of antineoplastic agents, and included extramedullary hematopoiesis, hypocellularity of the bone marrow, and thymic depletion.

At higher doses, toxicological effects were largely the same, but were increased in severity, particularly in the females, and many were typical for oncology agents. In dogs, a dose of 100 mg/kg/day (the highest dose tested) was determined to be the highest non-severely toxic dose (HNSTD). Findings in this study, primarily seen at 50 and 100 mg/kg/day, included emesis, slightly lower weight gains, increases in red cells (males only), decreased white cell counts, and elevated liver enzymes. Histopathological changes were limited to decreased cellularity of the bone marrow. None of these changes were considered serious in nature, and all had resolved by the end of the recovery period. Yellow hair coat, a characteristic of X-82, was seen in both species.

A phototoxicity study conducted in guinea pigs at 30 and 120 mg/kg found that X-82 caused transient erythema for up to 3 hours post exposure to ultraviolet light and is therefore, phototoxic in this species.

Two further repeat dose toxicology studies were also performed in rats and dogs. The first was a 26 week study in rats and the other was a 39 week study in dogs.

The 26 week rat study concluded that administration of X-82 to rats for up to 182 consecutive days at 5, 10, or 20 mg/kg/day in males and 1, 3, or 10 mg/kg/day in females did not result in adverse effects at any dose level. Following 182 days of dosing, minor X-82-related effects included increased body weight and body weight gain in animals at all dose levels, minimally decreased red blood cell count and minimally increased mean corpuscular volume and mean corpuscular hemoglobin in females given 10 mg/kg/day and males given 20 mg/kg/day, increased adrenal gland weights in females given 10 mg/kg/day, increased vacuolation in adrenal cortical cells in males given ≥10 mg/kg/day and females given 10 mg/kg/day, decreased cellularity in the bone marrow in males given ≥10 mg/kg/day and females given 10 mg/kg/day, and increased mast cells in sinuses of the mesenteric lymph node in males given ≥10 mg/kg/day and females given 10 mg/kg/day. The no observed adverse effect level (NOAEL) is 20 mg/kg/day for males and 10 mg/kg/day for females.

Likewise the 39 week dog study at 12.5, 25, or 50 mg/kg/day of X-82 concluded that the only adverse effect was tubular degeneration/atrophy in the testes at ≥12.5 mg/kg/day observed at interim or terminal sacrifice. Other minor, nonadverse, X-82-related effects included reduced intraluminal sperm in epididymis in one male at 12.5 mg/kg/day (interim sacrifice only) and yellow discoloration of the haircoat, minor protein concentration changes, decreased testis and epididymis weights, cellular debris and/or reduced intraluminal sperm in the epididymis, increased extramedullary hematopoiesis in the spleen, and hypocellular bone marrow for animals given ≥25 mg/kg/day. Based on these results, the no observed adverse effect level (NOAEL) of X-82, when administered for at least 39 weeks, is 50 mg/kg/day for females and was not achieved for males.

Additional information on the X-82 toxicology studies conducted to date is provided in the Investigator's Brochure (IB).

3.4.1.2 Pharmacokinetics

After a single dose with a suspension formulation of X-82, the measures of exposure, C_{max} and AUC_{0-t} or AUC_{0-24} increased with increasing dose for X-82, although the increases were not linear at the highest dose. X-297, the major metabolite, is rapidly produced and absorbed. After 7 or 28 days of repeated dosing, the values for C_{max} and AUC_{0-24} were similar or lower than on Day 1. On Day 1 in the rat study values for $t_{1/2}$ ranged from 2.8 to 5.0 hr for X-82 and from 2.6 to 8.6 hr for X-297. For dogs on Day 1, the mean values for $t_{1/2}$ ranged from 1.5 to 2.2 hr for X-82 and from 1.5 to 3.4 hr for X-297. In a tissue distribution study in mice, the concentrations of X-82 were similar in the plasma and tumor following administration of the suspension formulation. The concentrations in the liver and kidney were higher than the plasma concentration, indicating probable involvement in the metabolism and elimination of X-82. The concentrations in the fat, lung, heart, and spleen were similar or slightly lower than the plasma, and concentrations in the muscle and brain were approximately 40% and 6% of the plasma concentrations.

The plasma protein binding of X-82 was determined *in vitro*. There was no apparent dependence of % free drug on concentration in any of the species evaluated. In rats, the % free X-82 was approximately 0.3%. For mice, the % free X-82 was approximately 1.5%. For dogs, monkeys, and humans, the % free X-82 was approximately 2%. These results indicate high protein binding.

The metabolism of X-82 was studied in vitro using liver microsomes from dogs, monkeys and humans. The rates of metabolism were similar for dog and human microsomes, and the rate of metabolism was substantially faster for monkey microsomes. LC/MS/MS analysis revealed a total of 26 metabolites. There were no human-specific metabolites; however, neither dog nor monkey microsomes produced all 20 of the metabolites observed with human microsomes. Qualitatively, the major metabolites were C17, formed by hydroxylation plus hydrogenation; C18, formed by dihydroxylation; and C20 (X-297), formed by N-demethylation.

Inhibition of cytochrome P450 isozymes was assessed *in vitro* in pooled human liver microsomes by determining the effect of X-82 (10 µM) on the metabolism of the selective substrates phenacetin (CYP1A2), bufurarol (CYP2D6), diclofenac (2C9), (S)-mephenytoin (2C19), and midazolam (CYP3A4). The results suggest that X-82 has minimal potential to inhibit 3A4, 2D6, 2C19 or 1A2. However, approximately 55% inhibition of CYP2C9 activity was observed at 10 µM of X-82, which is >5 times the mean C_{max} (1.9 µM) of subjects at the saturation doses of 400 – 800 mg qd. X-82 is primarily metabolized by CYP3A4 and thus its concurrent use with potent CYP3A4 inhibitors or inducers should be avoided.

A tablet formulation of X-82 with dosage strengths of 50 mg and 100 mg was developed in order to improve the absorption/ exposure achieved with X-82. The tablet formulation was administered orally to dogs under both fed and fasted conditions and was compared with the 100 mg capsule formulation administered under fasted conditions, since that is how the drug was administered in the clinic. The 100 mg tablet under fed and fasted conditions resulted in an AUC_{0-t} that was approximately 3.5 - 4.8x and 2.6 - 3.6x higher, respectively, than that observed

with the 100 mg capsule. Exposures with 2 x 50 mg tablets were generally similar to those observed with the 100 mg tablet.

3.4.1.3 Pharmacodynamic Studies

In a diverse panel of human tumor nude mouse xenograft models, X-82 displayed comparable activity to sunitinib with respect to tumor growth inhibition. Models of renal cell, colon, pancreatic, melanoma, and leukemia were studied. In these studies the minimum effective dose that gave at least 50% inhibition of tumor growth in a sensitive model was 40 mg/kg BID. The dose of X-82 that induced a maximum effect (complete tumor stasis or regression) in most xenograft models was 160 mg/kg BID.

The exposure of X-82 as measured by AUC *in vivo* in nude mice at the maximally effective dose was 67,688 ng.hr/ml. In female rats an STD_{10} was observed at an AUC of 160,418 ng.hr/ml. Thus, there was little evidence of toxicity in rats at exposures 2.4 times the maximum efficacious exposure in mice. At the minimum effective dose of X-82 in a relevant renal cell carcinoma (RCC) xenograft model 53% inhibition of tumor growth was observed at an exposure calculated to be 9.4 times lower than the STD_{10} in female rats. These data suggest a very high safety window for X-82 that, if translatable to human, could result in maximum biologic activity with reduced toxicity.

The effects of X-82 on the development of proliferative diabetic retinopathy (PDR) was investigated in a murine model in which oxygen is used to induce angiogenesis and subsequent ischemic retinopathy. X-82 was able to reduce the angiogenic response by 71.1% compared to controls in this model. Furthermore, the measurement of X-82 concentrations also showed that the plasma and retina concentrations of X-82 were similar and thus X-82 can reach the retina via the leaky blood vessels seen in this model of PDR.

3.4.1.4 X-82 Phase 1 Study in Subjects with Advanced Solid Tumors

X-82 is currently being evaluated in a Phase 1 dose-escalation study designed to evaluate safety, tolerability, and pharmacokinetics in subjects with advanced solid tumors, under IND 108,192 sponsored by Tyrogenex. In the 52 study subjects enrolled at the time the current protocol was prepared, generally mild adverse events have been reported. The most frequently reported adverse events have been fatigue, nausea, vomiting, diarrhea, and hypertension. A maximum tolerated dose (MTD) has not been reached in this ongoing study.

Early data from this study suggest activity of X-82 in this study population, with some response to treatment.

Preliminary PK data show that the half-life of X-82 in humans is <9 hours at oral doses up to 800 mg per day. In general, there is no significant accumulation or induction after 21 days of daily dosing as the exposure curves on Days 1 and 22 are generally similar. Between 50 mg and 400 mg qd with the tablet formulation, the exposure increased with dose. But from 400 mg to 800 mg qd, there was little increase in exposure, suggesting absorption saturation occurs at doses close to 400 mg qd. The mean C_{max} and $AUC_{0\text{-}24h}$ observed in subjects at doses of 400 – 800 mg qd are 852 ng/ml and 8609 ng.hr/ml, respectively. However, doses greater than 100 mg once a day result in 12-hour plasma levels >100ng/ml, the minimum exposure required for efficacy in

the pre-clinical anti-angiogenesis model. At 100 mg qd, the mean C_{max} and AUC_{0-24h} are 315 ng/ml and 3130 ng.hr/ml, respectively.

3.4.1.5 X-82 Phase 1 Study in Subjects with Neovascular AMD

Twenty-nine previously treated subjects and 6 treatment naive subjects with wet AMD were enrolled under IND 116,264, Sponsored by Tyrogenex, Inc. These subjects received X-82 for up to 6 months at the following doses: 50 mg qod (3 subjects), 50 mg qd (8 subjects), 100 mg qod (4 subjects), 100 mg qd (10 subjects), 200 mg qd (7 subjects) and 300 mg qd (3 subjects). Subjects were seen every 4 weeks and underwent ETDRS VA measurement and SD-OCT for assessment on the need for Lucentis rescue therapy at each visit. SD-OCT images were read by the Digital Angiographic Reading Center (DARC), which acted as the independent reading center (IRC).

All 35 patients maintained or improved on their baseline visual acuity scores. Of these, 25 subjects completed the full 24 week treatment period and 15 (60%) of these subjects did not require any rescue therapy with Lucentis during the entire treatment period. Eight subjects (1 who received 100 mg, 5 who received 200 mg and 2 who received 300 mg) experienced significant reductions in fluid on SD-OCT within the first weeks of starting X-82 and these observations were confirmed by the IRC. Four subjects experienced transaminase elevations, one of which normalized while on treatment and the remaining three returned to normal when X-82 was discontinued. There was no dose relationship to these cases (1 case at 50 mg daily, 1 at 100 mg every other day, 1 at 100 mg daily and 1 at 200 mg) and none were associated with any other laboratory abnormality or clinical symptoms. Two patients on the 300 mg doses discontinued treatment due to gastrointestinal symptoms - one case of mild nausea and anorexia and one of a grade 2 diarrhea.

3.4.1.6 A Pharmacokinetic and Food Effect Study in Healthy Volunteers aged 50 and Over.

A recently completed study, X82-OPH-PK01, examined the urinary excretion of X-82 and its metabolite X-297 in healthy elderly subjects during administration of 100mg, 200 mg and 400 mg X-82 QD per os. The effects of renal function on total apparent clearance and renal clearance of X-82 and X-297 were also assessed. The study found that the cumulative amount of X-82 and X-297 excreted in the urine was much less than 1% and less than 2% of the 200 mg oral dose (highest phase 2 dose) of X-82, respectively. These results suggest renal elimination is not a major pathway for clearance of X-82 or its metabolite X-297. Measures of plasma exposure to X-82 and its metabolite, X-297 (i.e., maximum plasma concentrations and AUC) did not increase with decreasing renal function as assessed by creatinine clearance or eGFR. There also was no discernible relationship between creatinine clearance or eGFR and apparent oral clearance (CL/F) of X-82. There did not appear to be any discernible relationship between CLcr and the renal clearance of X-82 or X-297. Nor did there appear to be any relationship between renal clearance of X-82 and X-297 and age in healthy subjects ranging in age from 50 to 81 years of age. Thus, there is little evidence that renal function will influence the pharmacokinetics of X-82 or its metabolite, X-297.

3.4.1.7 Rationale for Phase 2 Clinical Trial of X-82 in Neovascular AMD

The stability of visual acuity, accompanied by changes in the SD-OCT images (fluid reductions) and relative infrequency of rescue therapy described in the phase 1 study above, suggests that

further investigation of the potential efficacy of oral X-82 in the treatment of wet AMD is warranted. The phase 1 study data support the conduct of a further randomized controlled clinical trial in subjects with previously treated nAMD. At least 132 subjects with neovascular AMD will participate in this comparative study. X-82 tablets (or matching placebo tablets) will be administered orally at doses of 50 mg qd, 100 mg qd and 200 mg qd.

4 STUDY OBJECTIVE

The objective of this study is to evaluate the efficacy and safety of X-82 at three doses, in subjects with wet AMD as determined by a comparison of the mean ETDRS visual acuity scores at Week 52.

5 STUDY DESIGN

This is a randomized, double-masked, placebo-controlled study in which at least 132 subjects will be randomized to receive either 50 mg, 100 mg or 200 mg of X-82, or matching placebo tablets daily for 52 weeks. Subjects requiring frequent injections of ivt anti-VEGF (an interval no greater than 8 weeks) and with the presence of any macular fluid and macular thickness on SD-OCT will receive a further injection of anti-VEGF during Screening Visit 1 and return for Screening Visit 2 to document a reduction in macular fluid or macular thickness, which will be confirmed by the Independent Reading Center (IRC). If a subject does not demonstrate any reduction of macular fluid or macular thickness at Screening Visit 2 and the investigator believes the subject may not have had enough time to achieve a reduction, subjects may be re-screened for Screening Visit 2 as long as the visit occurs within the protocol specified window [Day -14 (+/- 7 days)]. Subjects with a reduction in macular fluid or macular thickness will undergo additional screening assessments and be enrolled in to the study. Subjects will receive a further injection of anti-VEGF at Day -1 and start study treatment the following day. All subjects will remain on study treatment for 52 weeks and be assessed for the need for further injections of anti-VEGF every 4 weeks for that period.

5.1 SAMPLE SIZE, AND NUMBER AND LOCATION OF SITES

At least one hundred and thirty two (132) subjects will be randomized to either 50, 100 or 200 mg X-82 versus placebo qd in a 1:1:1:1 ratio (33:33:33:33 subjects) at 35 to 45 sites in the US. As much as a 20% rate of early discontinuation is accounted for in the power calculations. (See Section 11.3).

6 INVESTIGATIONAL TREATMENT (X-82) AND CONCOMITANT MEDICATIONS

6.1 50 MG AND 100 MG X-82 AND PLACEBO TABLETS

X-82 (50 mg and 100 mg doses) and matching placebo are formulated as identical round orange tablets and are provided in a 60 cc round high density polyethylene (HDPE) bottle containing 30 tablets, a desiccant canister and sealed with a white PP child-resistant (CR) cap with a heat-induction sealed inner liner.

The tablets should be stored at room temperature (15°C-30°/59°F-86°F).

6.2 X-82 DOSING

In this clinical trial, X-82 or matching placebo, will be administered per os (po) at a dose of 50 mg, 100 mg, or 200 mg, or matching placebo tablets qd. Subjects will be instructed to take one tablet from each of the two bottles provided. Subjects randomized to placebo will be dispensed with two bottles of placebo; subjects assigned to 50 mg will receive one bottle of 50 mg tablets and one bottle of placebo tablets: subjects assigned to 100 mg will receive two bottles of 50 mg tablets; subjects assigned to 200 mg will receive two bottles of 100 mg tablets.

The tablets should be taken with food, preferably at the same time each day. The subjects should note if the study medication was taken with a meal. No alcoholic beverages may be consumed during the 2 hours prior to taking their study medication and subjects must abstain from consuming any alcoholic beverages for a minimum of 2 hours after taking their study medication. Subjects should confirm at each visit that the study medication was not consumed within 2 hours of consuming a beverage containing alcohol.

The time of day for administration of study tablets should be consistent for each subject. If the subject misses a dose of study medication, the subject should take the dose as soon as possible, but not less than 12 hours before the next dose is scheduled for administration. If the next dose is scheduled for less than 12 hours, the subject should skip the missed dose and take the next dose as scheduled. Subjects will keep a dosing diary for the duration of the study and this should be reviewed with the subjects at each visit. X-82 is 1000 times more soluble in ethanol than in aqueous buffers and therefore the consumption of X-82 with alcohol could increase the systemic absorption of X-82 by increasing its solubility in the GI tract.

6.3 RE-TREATMENT WITH ANTI-VEGF

In addition to the experimental drug, X-82 or matching placebo, subjects will be assessed on the need for injections of ivt anti-VEGF. Injections may be Avastin, Lucentis or Eylea, but should remain the same treatment as the subjects were receiving at the time of enrollment into this study and should be based on the following criteria:

> Any increase in macular fluid or macular thickness (or the presence of any fluid if the Screening Visit 2 scan was completely dry) compared to the SD-OCT scan observed at Screening Visit 2. This includes visible subretinal fluid, visible intraretinal cysts, or an increase in size or new PED (documented by SD-OCT images).
>
> or
>
> New or increased macular hemorrhage (documented by fundus photographs)

Any vision loss, which is not accompanied by the presence of fluid or hemorrhage, should be investigated (by FA or other means) to determine the cause.

Images will be transmitted to the reading center for review.

6.4 CONCOMITANT MEDICATIONS

All concomitant medications taken by the study subjects within 7 days prior to the first dose of study drug will be documented at baseline. Additionally, at each visit, the investigator will ask

the subject about any new medications he/she is taking or has taken after the start of the study drug and this information will also be documented in the study case report forms.

6.4.1 Prohibited Concomitant Medications

The wash out period for non-herbal medications is 29 days (starting at Screening Visit 1) and 7 days for herbal medications. The following non-study treatments are prohibited during study participation from Day -29 (and Day -7 for herbal medications):

- Radiation therapy, hormonal therapy for cancer (with the exception of LHRH agonists for prostate cancer), cancer chemotherapy, cancer immunotherapy or other biologic therapy.
- Other investigational drugs within thirty (30) days or 5 half-lives, whichever is longer, of Day -1.
- Chronic treatment (> 7 days) with systemic steroids (dose >10 mg daily or 20 mg every other day of prednisolone or equivalent) or other immunosuppressive agents. Topical or inhaled corticosteroids are allowed.
- Concomitant treatment with any medication which may cause QT prolongation or torsade de pointes should be used with caution. A list of these medications is provided in Appendix 2.
- Common inhibitors, inducers and substrates of P450, including CYP3A and potent CYP3A4 inhibitors or inducers (see Appendix 3 for full list of such drugs).
- St. John's wort is not permitted throughout the trial. Subjects should discontinue use at least 7 days prior to the first dose of study drug.
- Warfarin and other coumarin anticoagulants (e.g. acenocoumarol, phenprocoumon, fluindione) are not permitted throughout the trial. If treatment with a coumarin anticoagulant is initiated during the trial, X-82 must be discontinued immediately.

7 STUDY POPULATION

7.1 INCLUSION CRITERIA

Subjects must meet the following criteria:

1. Participants must have neovascular AMD (Fluid must be present at Day -29 and the IRC must confirm eligibility of SD-OCT images **prior** to randomization) which has been diagnosed and treated with anti-VEGF in one or both eyes for at least 6 months prior to joining the study and has required at least two prior injections of ivt anti-VEGF at intervals of not greater than 8 weeks (+ 7 days) for the past two injections in the eye that is selected to be the study eye *(the injection to be administered on Day -29 will be, at minimum, the third such injection and these final three injections must be with the same ivt anti-VEGF therapy)*.
2. Must have demonstrated the ability to achieve a reduction in macular fluid or macular thickness in the study eye at Screening Visit 2 (Day -14) following an injection of ivt

anti-VEGF at Screening Visit 1. ***(General thickening of the retina without visible cystic changes or subretinal fluid is not exclusionary for the study at Screening Visit 2.)***

3. Early Treatment Diabetic Retinopathy (ETDRS) Best Corrected Visual Acuity (BCVA) of 25 letters (20/320) or better in both eyes.
4. Age ≥ 50 years.
5. Adequate bone marrow function:
   a) Absolute neutrophil count (neutrophils and bands) ≥2500 cells/mm3;
   b) Platelet count ≥130,000 cells/mm3;
   c) Hemoglobin, ≥10.0 g/dL;
6. Adequate hepatic function:
   a) Total bilirubin within the institutional ULN (Subjects with an increased total bilirubin secondary to a genetically confirmed diagnosis of Gilbert's syndrome may be considered for inclusion after discussion with the medical monitor);
   b) Alanine and aspartate aminotransferase (ALT/AST) ≤2 times the institutional ULN
7. Adequate renal function; calculated GFR of ≥ 30 mL/min/1.73 m^2 (CKD-EPI calculation).
8. TSH and free T4 within normal limits (unless approved by Study Medical Monitor).
9. Ability to swallow and retain oral medication.
10. Willing and able to provide written informed consent, comply with the investigational study protocol and return for all study visits and continue to receive the same anti-VEGF therapy they received at Screening Visit 1 on an as needed basis.

7.2 EXCLUSION CRITERIA

Subjects who meet any of the following criteria will be excluded from study participation:

1. Vitrectomy to the study eye within 30 days of Screening Visit 1.
2. CNV due to causes other than AMD, including ocular histoplasmosis syndrome, angioid streaks, multifocal choroiditis, choroidal rupture, or pathologic myopia (spherical equivalent ≥ -8 diopters).
3. Proliferative diabetic retinopathy in either eye.
4. In the opinion of the investigator, any significant disease in the study eye that could compromise best-corrected visual acuity, e.g., glaucoma with documented visual field loss, severe uncontrolled glaucoma, clinically significant diabetic macular edema, proliferative diabetic retinopathy, ischemic optic neuropathy, uveitis, retinal vasculopathies including retinal vein occlusion, retinitis pigmentosa, etc.
5. Trabeculectomy or aqueous shunt or valve in the study eye.
6. Intraocular surgery in the study eye within three months of Day -1.

7. Inadequate pupillary dilation or significant media opacities in the study eye, which may interfere with visual acuity measurement or evaluation of the posterior segment, including fundus photography.

8. Use of any investigational agent or participation in any other clinical trial of an investigational agent or investigational therapy within thirty (30) days or 5 half-lives, whichever is longer, of Day -1.

9. Females of child bearing potential that are pregnant or not using medically acceptable contraception; males unwilling to take adequate contraceptive measures. Females that are breastfeeding are also excluded (see Section 9.8.11 for details on contraception requirements).

10. Serious allergy to or prior significant adverse reaction to fluorescein. Note that subjects that have experienced nausea or itching from the fluorescein that was treatable with diphenhydramine or anti-emetics that are not prohibited as concomitant medications for this study are not excluded.

11. Any history of cerebrovascular accident (CVA) or transient ischemic attack within 12 months prior to Screening Visit 1.

12. History of myocardial infarction, ventricular arrhythmia, stable/unstable angina, symptomatic congestive heart failure, or coronary/peripheral artery bypass graft or stenting, or other significant cardiac disease within 12 months prior to Screening Visit 1.

13. Any history of arterial or venous thrombosis/thromboembolic event, including pulmonary embolism, within the 12 months prior to Screening Visit 1.

14. Any episode of atrial fibrillation in the 12 months prior to Screening Visit 1.

15. Uncontrolled hypertension (BP > 160/100, despite pharmacological intervention).

16. QTcF ≥450 msec (males) or ≥ 470 msec (females) or subjects with a history of risk factors for Torsades de Pointes (e.g. familial long QT syndrome, left ventricular hypertrophy, slow heart rate [<45 bpm] or other clinically significant abnormalities, as determined by the investigator.

17. Current treatment with warfarin or other coumarin anticoagulants.

18. Use of any drugs excluded in Section 6.4.1 (Prohibited concomitant medications and shown in Appendix 3.

19. Any surgical procedure requiring an in-hospital stay within 28 days of Screening Visit 1.

20. Invasive dental surgery within 28 days of Day-1; any planned invasive dental surgery during study participation.

21. Presence of active gastrointestinal (GI) disease or other condition that will interfere significantly with the absorption, distribution, metabolism, or excretion of X-82.

22. Serious active infection, other serious medical condition, laboratory abnormality or any other condition that would impair the ability of the subject to administer the investigational drug or to adhere to the study protocol requirements.

23. Presence of any condition which, in the judgment of the investigator, would prevent the subject from completing the study.

24. Prior exposure to X-82.

25. History of allergy or intolerance to Eylea, Lucentis or Avastin, or intolerance to the excipients in X-82 or Eylea, Lucentis or Avastin.

8 PHARMACOKINETICS

8.1 PHARMACOKINETIC SAMPLING

Pharmacokinetic sampling will be performed in subjects who agree to participate to the three extended visits from all dose groups. Blood samples for pK analysis will be obtained on three separate occasions at the Week 4 Visit, Week 16 ***or*** Week 20 Visit, ***and*** Week 40 ***or*** Week 44, ***or*** Week 48 Visit. At each of these visits, the blood collection is to take place prior to the administration of X-82 (0 hr), then again at 4 hrs and finally again at between 6 and 8 hours post X-82 dose. The Visit number, date and times of the blood draws and date and time of X-82 dosing are to be recorded in the source documents.

Subjects must fast from food for at least 3 hours prior to blood draw. Subjects are permitted to take prescription medications on the morning of the PK visit, but must not take their study drug dose until after their first blood draw (0 hr). These extended pK sampling visits are not mandatory, but it is hoped at least half of all participating patients will agree to them.

8.2 PHARMACOKINETIC DATA ANALYSES

X-82 plasma pharmacokinetic parameters will be derived from X-82 plasma concentration-time data for each dose group using noncompartmental methods.

9 SUBJECT ENROLLMENT, TREATMENT AND SCHEDULE OF VISITS

9.1 SCREENING AND INFORMED CONSENT

The investigator will explain the study purpose, procedures, and subject's responsibilities to the potential participant. The subject's willingness and ability to meet the follow-up requirements will be determined and written informed consent will be obtained. The consenting process is to be documented in the source documents. The subject will sign and date the informed consent form, and the investigator or his/her representative will also sign and date the consent form. The original informed consent form will be retained with the subject records; a copy will be provided to the subject.

Written informed consent must be obtained before any protocol specific procedures are performed. The subjects will be consented prior to the first anti-VEGF injection at day -29 (Screening Visit 1) and some subjects may be consented prior to any prescreening period if the subjects' standard of care or management is changed with a view to enrolling them in this study. This protocol requires that subjects demonstrate a reduction in macular fluid or macular thickness after receiving this first anti-VEGF injection and only after the demonstration of a reduction in macular fluid or macular thickness on SD-OCT (which must be confirmed by the reading center) can the subject be enrolled into the study after completion of the Screening Visit 2 procedures. ***However, because some of the laboratory analyses take more than a week for the results to become available, the subjects having an OCT for confirmation of a reduction in macular fluid or macular thickness later than Day -14, should still have their visit 2 blood draw and ECGs performed no later than Day -14.***

Screening will include ECG, laboratory analyses, vital signs, pregnancy test for women of childbearing potential, (these assessments may be performed at either screening visit, but the schedule presented below is preferred) visual acuity, IOP, slit lamp and funduscopic examinations and must be performed prior to the second anti-VEGF injection which will occur on Day -1.

9.2 DAY -29: SCREENING VISIT 1 – ANTI-VEGF TREATMENT

After providing informed consent (if not already provided earlier for subjects being prescreened), and confirming the subject requires an anti-VEGF injection due to the presence of any subretinal, intraretinal, or sub-RPE fluid on SD-OCT, the following assessments should be completed:

- Demographics
- Eligibility criteria
- Medical History
- Ophthalmic History
- Concomitant medications and prior AMD treatments review

If the subject fulfills these criteria, they will receive an anti-VEGF injection and they will be asked to return 14 days (+/- 7 days) later to have a further SD-OCT image taken to demonstrate a response to ivt anti-VEGF within 14 days (+/- 7 days) of receiving an injection.

9.3 DAY -14 (±7): SCREENING VISIT 2 - CONFIRMATION OF RESPONSE TO ANTI-VEGF

Subjects who demonstrate a reduction in macular fluid or macular thickness at Screening Visit 2 will then complete the remaining screening procedures to confirm they meet the remainder of the study eligibility criteria and if so, be scheduled to return for another anti-VEGF injection on Day -1 of the protocol. Reduction in macular fluid or macular thickness will be documented in SD-OCT images from Screening Visit 2 as compared to SD-OCT images from Screening Visit 1. Images will be transmitted to the reading center for further review.

The minus 7 day window is permitted for subjects who are considered likely to demonstrate a reduction in macular fluid or macular thickness earlier than 14 days post-injection and the plus 7 day window for subjects who were not able to demonstrate a reduction in macular fluid or

macular thickness at Day -14. The window is particularly for subjects for whom this is second screening attempt who had fluid at Day -14 on the previous attempt. If a re-screen visit is scheduled, labs and ECG should still be performed at the first visit to ensure that the results will be available for enrollment on Day -1.

ALL OPHTHALMIC PARAMETERS WILL BE FOR BOTH EYES THROUGHOUT THE STUDY.

- Best corrected visual acuity using ETDRS (VA) at 4 meters performed prior to dilating eyes (VA)
- Spectral Domain Optical coherence tomography (SD-OCT) – If the Investigator determines there is a reduction in macular fluid or macular thickness, continue with Screening procedures. If the Investigator decides to schedule a re-screen visit, labs and ECG should be performed, otherwise this subject will be deemed a screen failure.
- Height, weight, BP, and pulse will be recorded.
- ECG
- Laboratory Assessments (see Section 9.8.3 to 9.8.6)
- Urinalysis (and pregnancy test if appropriate - see Section 9.8.7
- Ophthalmic examination including slit lamp and funduscopy (Ophthalmic Exam)
- Intraocular pressure (IOP)
- Fluorescein angiography (FA)
- Color Fundus Photographs (Photos)
- Record adverse events
- Record concomitant medications

9.4 DAY -1 [28 DAYS AFTER DAY -29 (±3)]: RANDOMIZATION

Eligible subjects who demonstrate a reduction of macular fluid or macular thickness at Screening Visit 2 and met all study criteria will return on Day -1 to be randomized to study treatment and receive a further injection of anti-VEGF. Subjects will receive their assigned study medication and dosing compliance log and be told to commence taking the medication the following day with food (Day 1) and to document the dose on the compliance log every day.

- Mandatory ivt anti-VEGF injection
- VA
- Ophthalmic exam
- IOP
- SD-OCT
- Subject dispensed study medication and dosing compliance log
- Record adverse events
- Record concomitant medications

9.5 WEEKS 4 TO 48 (±7)

Participants will return every 4 weeks for the following assessments on both eyes:

- VA
- Ophthalmic exam

- Vital Signs
- IOP
- SD-OCT
- Laboratory Assessments and Urinalysis
- Pharmacokinetic (pK) Sampling to occur at 3 timepoints:
  Week 4 ***and*** Week 16 ***or*** 20 **and** Week 40, ***or*** 44, ***or*** 48)
- Assess the need for reinjection with ivt anti-VEGF
- Review dosing compliance log from the previous month
- Subject dispensed study medication and new dosing compliance log
- Record adverse events
- Record concomitant medications
- ECG (Weeks 4, 12, 20, 28, 36, and 44)

9.6 WEEK 52 AND EARLY TERMINATION (±7)

Participants will return at week 52 for the following assessments on both eyes:

- VA
- Ophthalmic exam
- Weight and Vital Signs
- IOP
- SD-OCT
- FA and Photos
- Laboratory Assessments and Urinalysis
- PG Sampling
- ECG
- Review dosing compliance log from the previous month
- Assess the need for reinjection with ivt anti-VEGF
- Record adverse events
- Record concomitant medications

9.7 WEEK 56: (OR ONE MONTH POST-X82 TREATMENT) FOLLOW-UP VISIT (±7)

Participants will return 4 weeks after completing treatment with study drug for the following assessments on both eyes:

- VA
- Ophthalmic exam
- Vital Signs
- IOP
- SD-OCT
- Laboratory Assessments and Urinalysis
- Assess the need for anti-VEGF treatment as part of subject's standard of care
- Record adverse events
- Record concomitant medications

9.8 CLINICAL PARAMETERS AND DIAGNOSTIC TESTS

9.8.1 History and Vital Signs

A medical history, height and weight will be recorded at Screening. Weight will be repeated again at Week 52. Vital signs (blood pressure and pulse) will be recorded at Screening and every study visit from Week 4 onwards.

9.8.2 Electrocardiogram (ECG)

At Screening, Week 4, 12, 20, 28, 36, and 44 and Week 52, each subject will undergo a 12-lead electrocardiogram (ECG).

9.8.3 Complete Blood Count (CBC) with Differential

CBC plus differential panel that includes white blood cells, differential, hematocrit, hemoglobin and platelets will be performed at Screening, and every study visit from Week 4 onwards.

9.8.4 Comprehensive Metabolic Profile (CMP)

A CMP that includes blood glucose, blood urea nitrogen (BUN), creatinine, sodium, potassium, magnesium, chloride, calcium, phosphate, carbon dioxide (CO_2), alkaline phosphatase, AST (SGOT), ALT (SGPT), total bilirubin, total protein and albumin will be performed at Screening and every study visit from Week 4 onwards.

9.8.5 Thyroid Function

Serum TSH, total T3 and free T4 levels will be determined at Screening and then Weeks 4, 12, 28 and 52.

9.8.6 Additional Serum Tests: Lipase, Amylase and Creatine Kinase Measurement

Serum tests for lipase, amylase and creatine kinase will be determined at the Screening and every study visit from Week 4 onwards.

9.8.7 Urinalysis

A urine dipstick will be performed at Screening and every study visit from Week 4 onwards. If abnormalities are present on urine dipstick, additional testing (e.g., microscopic examination, urinary protein: creatinine ratio, etc.) should be done as clinically indicated. Urine pregnancy test will be performed at Screening Visit 2, Day -1 and every study visit for women of childbearing potential. If the pregnancy test is positive, the subject will be screen failed or discontinued from the study.

9.8.8 Pharmacokinetic (PK) Sampling

If subjects consent to participate in pK sampling, blood samples for pK analyses will be obtained on the three separate visits: 1) Week 4 Visit. 2) Week 16 or Week 20 Visit, and 3) Week 40 or Week 44 or Week 48 Visit. At each of these visits, the blood samples are to be drawn at three different time points: 1) Prior to the administration of X-82 [0 hour and then followed by breakfast], 2) 4 hours post X-82 dose, and 3) 6-8 hours post X-82 dose. The acceptable window is +/- 30 minutes for the 4-hour time point. The acceptable window for the 6 to 8 hour sample is 5.5 to 8.5 hours.

9.8.9 Pharmacogenetic (PG) Sampling

If subjects consent to participate in PG sampling, blood will be drawn to obtain germline DNA samples at the Week 52 or Early Termination Visit for possible PG analyses in the event that outliers with respect to efficacy, tolerability/safety or exposure are identified.

9.8.10 OPHTHALMIC ASSESSMENTS

9.8.10.1 Best Corrected Visual Acuity

Manifest refraction and VA measurement must be performed according to the standard procedure originally developed for ETDRS and adapted for the Age Related Eye Disease Study (AREDS) protocol. VA testing by ETDRS protocol is detailed in Appendix 7. VA will be tested by trial certified examiners on both eyes, in trial certified examination rooms at every visit.

9.8.10.2 Intraocular Pressure (IOP)

IOP will be measured using applanation or tonopen on both eyes at every visit from Screening Visit 2 onward.

9.8.10.3 Slit Lamp Examination and Funduscopy

A slit lamp examination and funduscopy will be performed on both eyes at every visit from Screening Visit 2 onward.

9.8.10.4 Spectral Domain Optical Coherence Tomography (SD-OCT)

Spectral domain OCT (SD-OCT) will be utilized to assess subretinal fluid, intraretinal thickening, and neovascular lesions on both eyes at each visit. At each 4 weekly visit the Investigator will review the participant's SD-OCT. All images will be sent to the reading center for masked assessment. The SD-OCT machine and technician will be certified by the Independent Reading Center (IRC) prior to study commencement.

The SD-OCT taken at Screening Visit 2 must be sent to the IRC for confirmation of eligibility within 24 hours of acquisition and confirmation of eligibility received **prior to randomization**. All other images should be sent to the IRC no more than 5 days after their acquisition, and in accordance with the protocol supplied by the IRC.

9.8.10.5 Fluorescein Angiography (FA) and Color Fundus Photographs

Fluorescein Angiograms (FAs) and Color Fundus Photographs (Photos) will be undertaken at screening and again at week 52. All FAs and Photos will be performed using digital fluorescein photography equipment and cameras certified by the IRC. The photographers undertaking FA and photos must be certified by the IRC prior to undertaking any angiograms on trial participants. The reading center will provide a protocol for image acquisition and transfer. This protocol must be strictly adhered to. All images must be transferred to the IRC within 5 day of obtaining them.

9.8.11 RESTRICTION ON THE LIFESTYLE OF SUBJECTS

9.8.11.1 Contraception Requirements

All subjects of childbearing potential must refrain from sperm/egg donation, be abstinent, if this is the usual and permanent life-style choice of the subject, or if engaged in sexual relations of child-bearing potential (for themselves or their partner), they must use effective contraception from the time of signing the informed consent form until at least 14 weeks after their last dose of study treatment.
For the purposes of this study, women of childbearing potential are defined as any female who has experienced menarche, and that does not meet one of the following conditions:

• Postmenopausal: 12 months of spontaneous amenorrhea

• 6 weeks after surgical bilateral oophorectomy with or without hysterectomy

• Post hysterectomy

For the purposes of the study, effective contraception is defined as follows:
For male subjects:

• Effective male contraception includes a vasectomy with negative semen analysis at Follow-up, or the use of condoms together with spermicidal foam/gel/film/ cream/suppository. Male subjects must also encourage their female partner to use effective contraception from the time of signing the informed consent until at least 14 weeks after the subject's last dose of study treatment. Effective contraceptive for the female partner includes: surgical sterilization (e.g., bilateral tubal ligation), hormonal contraception, intrauterine contraception/device, or barrier methods (female condom*, diaphragm, sponge, cervical cap) together with spermicidal foam/gel/film/cream/ suppository. Male subjects with partners that are pregnant must use condoms as contraception to ensure that the fetus is not exposed to the Study Drug.

For female subjects:
• Using 1 or more of the following acceptable methods of contraception: surgical sterilization (e.g., bilateral tubal ligation), hormonal contraception, intrauterine contraception/device, or any 2 barrier methods (a combination of male or female condom* with diaphragm, sponge, or cervical cap) together with spermicidal foam/gel/film/cream/suppository.

***Note: A female condom and a male condom should not be used together as friction between the two can result in either product failing**

9.8.11.2 Exposure to Sunlight

All subjects should be advised of the potential phototoxicity of X-82 and advised to avoid direct contact with sunlight by covering arms and legs and wearing a hat and sunglasses while taking the study medication.

10 INVESTIGATIONAL PRODUCT

X-82 will be administered orally as 50 mg and 100 mg tablets to provide either a 50 mg, 100mg or 200 mg dose.

Additional information can be found in the X-82 Investigator's Brochure.

10.1 LABELING, PACKAGING, AND SUPPLY

X-82 Tablets (50 mg and 100 mg) are provided to the sites in HDPE Bottles with one Sorbit ½ Gram Desiccant Canister. Thirty (30) tablets are included in each bottle. Each bottle is capped with a Child Resistant Closure with White Liner.

X-82 should be stored at room temperature (15ºC-30ºC/59ºF- 86ºF).

The following information will be pre-printed on the bottle label: Contents of the bottle, storage conditions, and lot number. The label will also contain a statement to conform with FDA Investigational New Drug (IND) requirements as follows:

"Caution: New Drug - Limited by Federal (US) law to investigational use".

All trial drugs must be kept in a secure place under appropriate storage conditions. Storage conditions for X-82 are included in the X-82 Investigator's Brochure.

The Sponsor or its representatives must be granted access on reasonable request to check drug storage, dispensing procedures, and accountability records.

10.2 PREPARATION AND ADMINISTRATION OF INVESTIGATIONAL PRODUCTS

X-82 will be self-administered by the subject. The investigator will instruct the subject to take the study drug exactly as specified in the protocol.

10.3 ACCOUNTABILITY OF INVESTIGATIONAL PRODUCTS

The PI (or designee) is responsible for accountability of all used and unused trial drug supplies at the site.

The Sponsor or designee will verify receipt of investigational product at the site during monitoring visit(s), and will conduct an inventory of remaining clinical trial supplies at the site close-out visit. All trial drug inventories must be made available for inspection by the monitor, Sponsor, or representatives of the aforementioned and regulatory agency inspectors upon request.

Dispensation of investigational product will be recorded in the source document and Drug Accountability Records.

At the end of the trial, a "Return Drug Form" will be completed by the site's monitor and will accompany the clinical trial supplies that are returned to the Sponsor (or designee). Clinical trial supplies must not be destroyed unless prior approval has been granted by the Sponsor or its representative.

10.4 SAFETY MONITORING RULES

Please refer also to the 'Guidance for Investigator' section of the Investigator's Brochure.

For the purposes of safety monitoring, baseline is defined as the pre-dose value on Day 1 or, if no pre-dose Day 1 result is available it is the pre-dose test performed closest to Day 1.

In addition to the standard monitoring of clinical safety parameters, the following guidelines are provided for the monitoring of selected parameters chosen based on preclinical and clinical observations.

Confirmation Guidance: At any time during the study (Treatment or Post-Treatment Periods), the initial clinical laboratory results meeting the safety monitoring criteria presented below must be confirmed by performing measurements (ideally in the same laboratory that performed the initial measurement) on new specimens. All new specimen collections should take place as soon as possible (ideally within 3 days of the initial collection).

Re-dosing Guidance: In general, subjects who do not meet the stopping rules based upon retest may continue dosing. However, the Investigator and the Medical Monitor (or appropriately qualified designee) should confer as to whether additional close monitoring of the subject is appropriate. If any of the stopping criteria described below (refer to Section 10.5) are met, the subject will be permanently discontinued from further treatment with Study Drug (X-82 or placebo), evaluated fully as outlined below and in consultation with the Sponsor Medical Monitor or appropriately qualified designee, and will be followed up in accordance with Section 12 of the protocol.

10.4.1 Safety Monitoring Rules for Liver Chemistry Tests

In the event of an ALT or AST measurement that is > 3 x ULN or > 2 x Baseline value, whichever is greater, at any time during the study (Treatment or Post-Treatment Period), the initial measurement(s) should be confirmed as described above in Section 10.4. Similarly, confirmatory measurements should also be performed if ALT or AST levels increase to 5 x ULN (following the initial meeting of each of those criteria). If confirmed, the Investigator and Medical Monitor will determine the frequency of monitoring and action to be taken with Study Drug.

Further Investigation into Liver Chemistry Elevations: For patients with confirmed ALT or AST levels > 3 x ULN or > 2 x Baseline value, whichever is greater, the following evaluations should be performed:

1. Obtain a more detailed history of symptoms and prior and concurrent diseases

2. Obtain further history for concomitant drug use (including nonprescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets

3. Obtain a history for exposure to environmental chemical agents and travel

4. Serology for viral hepatitis sources other than HBV (HAV IgM, HCV antibody, CMV IgM, and EBV antibody panel)

5. Serology for autoimmune hepatitis (e.g., antinuclear antibody [ANA])

Additional liver evaluations, including gastroenterology/hepatology consultations, hepatic CT or MRI scans, may be performed at the discretion of the Investigator, in consultation with the Sponsor Medical Monitor. Repetition of the above evaluations should be considered if a patient's ALT and/or AST levels progress over time.

10.5 STOPPING RULES FOR LIVER CHEMISTRY ELEVATIONS

In the event of confirmed laboratory results meeting the following criteria, and the event is without an alternative explanation as discussed with the Sponsor Medical Monitor, or designee, dosing of a patient with Study Drug (X-82 or placebo) will be stopped permanently. Values that are not confirmed due to failure to retest or missing lab values will be presumed confirmed:

1. ALT or AST > 8 x ULN, which is confirmed
2. ALT or AST > 5 x ULN, which is confirmed and persists for ≥ 2 weeks
3. ALT or AST > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if baseline value was > ULN), which is confirmed and total bilirubin > 2 x ULN or INR > 1.5
4. ALT or AST > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), which is confirmed and the new appearance (i.e., onset coincides with the changes in hepatic enzymes) of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or concomitant eosinophilia (> ULN)

10.6 DOSE MODIFICATIONS FOR TOXICITY

Dose modifications will not be permitted in this study due to its masked design and the use of placebo tablets in both active and placebo treated subjects.

11 STATISTICAL PLAN

11.1 EFFICACY OUTCOMES AND HYPOTHESES

The study's primary hypothesis is that participants who receive X-82 plus ivt anti-VEGF *prn* will have a non-inferior ETDRS visual acuity score after 52 weeks of treatment to the participants who receive ivt anti-VEGF monotherapy (ivt anti-VEGF *prn* plus placebo).

11.1.1 Primary Efficacy Outcome

The primary outcome is the change in visual acuity score from Day -1 to 52 Weeks after randomization in the study eye.

11.1.2 Secondary Efficacy Outcome

The secondary outcome is the number of ivt anti-VEGF injections during the first 52 Weeks after randomization in the study eye.

11.1.3 Other Efficacy Outcomes

- Proportion of subjects maintaining vision at 52 Weeks (losing < 15 letters on ETDRS chart)
- Mean changes in CNV, total and active lesion sizes on FA at 52 Weeks
- Mean changes in retinal thickness on SD-OCT at 52 Weeks
- Other variables derived from the SD-OCT measurements
- Time from Day 1 to first anti-VEGF injection
- Conversion of fellow eye by 52 Weeks in subjects enrolled with unilateral disease

11.2 SAFETY MEASURES

Incidence of serious adverse events (SAEs) and adverse events (AEs), laboratory assessments and ECG. All subjects who have received at least one dose of X-82 will be included in the safety population.

The trial will specifically report the incidence of events considered to be related to treatment with tyrosine kinase inhibitors.

11.3 SAMPLE SIZE JUSTIFICATION

Based on similarly designed trials with this outcome in this population of previously treated AMD subjects, the SD of the change in visual acuity was assumed equal to 15. However, upon recalculation of the sample size, the correct SD to reproduce the required sample size is 14.3. With a sample size of 132 subjects, the trial will have at least 80% power to conclude the non-inferiority of X-82 plus ivt anti-VEGF *prn* as compared to ivt anti-VEGF *prn* plus placebo in terms of visual acuity, using a non-inferiority margin equal to 9 ETDRS letters and a one-sided significance level of 0.05. This sample size was calculated assuming all doses are equally as efficacious, testing a difference in means for all 3 doses against placebo (i.e. using a randomization ratio of 3:1). Of note, this sample size calculation makes the conservative assumption that the dropout rate is as high as 20%, and that there is no treatment effect among dropouts; the required sample size is obtained by multiplying the randomized sample size by (1-dropout rate)^2. If assuming an allocation ratio of 1:1 to better examine the power of a pairwise comparison, there is 80% power accounting for a dropout rate up to 20% if the true SD is 11. Based on previous studies, a SD of less than 14 is reasonable [25].

11.4 TESTING PROCEDURE

Each dose will be tested against placebo using a Hochberg procedure. Let p_1, p_2 and p_3 be the *p*-values of the tests comparing each dose *vs.* placebo, with $p_1 \geq p_2 \geq p_3$. Let α be the significance level appropriate for the analysis, provided by the O'Brien-Fleming type Lan-DeMets alpha spending function, given the information fraction at the time of the analysis [26]. If $p_1 < \alpha$, the three doses are non-inferior to placebo and the choice of dose must be based on other considerations. If $p_1 > \alpha$ and $p_2 < \alpha/2$, the doses corresponding to p_2 and to p_3 are non-inferior to placebo. If $p_1 > \alpha$and $p_2 > \alpha/2$ and $p_3 < \alpha/3$, the dose corresponding to p_3 is non-inferior to placebo. If $p_1 > \alpha$ and $p_2 > \alpha/2$ and $p_3 > \alpha/3$, no dose can be declared non-inferior to placebo.

11.5 RANDOMIZATION

Randomization will be performed through an interactive web based system. Participants will be randomized to X-82 and placebo in a 1:1:1:1 ratio, using a dynamic minimization procedure

stratified by previous treatment schedule (every 6 weeks or less versus every 8 weeks) and anti-VEGF therapy. The dynamic minimization will use a stochastic treatment allocation algorithm based on the variance method; this implementation of minimization guarantees that all treatment allocations are stochastic.

11.6 ANALYSIS POPULATIONS

The Intent-to-Treat (ITT) population consists of all randomized subjects, grouped by treatment assigned by randomization. All efficacy analyses will be carried out on the ITT population.

The Per-Protocol (PP) population consists of all randomized subjects who do not present a major protocol violation, grouped by treatment actually received. Major protocol violations will be adjudicated by a committee of experts who will not have access to treatment allocations, prior to the database lock. A sensitivity analysis using the PP population will be performed on the primary and secondary efficacy outcomes of the trial.

The safety population will consist of all subjects treated, grouped by treatment group actually received. All safety analyses will be performed on the safety population.

11.7 INTERIM ANALYSES

11.7.1 Interim Analysis 1

An interim analysis is deemed necessary to enable the DSMB of the trial to perform a benefit/risk assessment including all efficacy and safety outcomes. This analysis will be conducted after 60 patients have reached their week 24 visit. The primary efficacy outcome of non-inferiority in change from randomization in VAS will be tested using an O'Brien-Fleming type Lan-DeMets alpha spending function, where the information fraction will be the percentage of patients that have completed their 52 week visit, though all available data will be used in the repeated measures model. There is no intention to stop early for efficacy, and the interim analysis will not be adequately powered to enable the DSMB to make such a recommendation. The spending function will however be used to adjust the significance level of the final analysis, given the interim analysis performed, should the trial continue unchanged. The adjustment has very little impact on the power of the trial, should the trial continue unchanged. If one or more of the doses of X-82 is stopped for any reason, the final analysis will make allowance for this adaptive design change by considering that the doses dropped would have failed to reach significance in the Hochberg procedure described in Section 11.4. This approach protects the significance level for each of the doses tested in the final analysis.

An O'Brien-Fleming type Lan-DeMets beta spending function (using beta of 20%) will be used to assess futility at the time of the interim analysis. The futility boundary will be non-binding and, as such, will be used for information only.

The available secondary efficacy outcome data of number of injections per year will also be presented to the DSMB at the time of interim analysis to guide decisions for dropping doses of X-82 or stopping the trial for futility or unfavorable risk/benefit ratio.

11.7.2 Interim Analysis 2

After the first interim analysis was conducted, it was determined an additional interim analysis will be necessary to enable the Sponsor to plan future trials of X82 in wet AMD or other indications. The second interim analysis will be reviewed by the DSMB and by a small group of individuals designated by the Sponsor.

The second interim analysis is planned to be performed once approximately 90% of all subjects have reached their week 36 visit. The primary efficacy outcome will be tested using the O-Brien-Fleming type Lan-Demets alpha spending function using the same approach as described in section 11.7.1. The calculation will take into consideration the first interim analysis, i.e. the first information fraction will be used in the calculation, along with the second information fraction. This accounts for the alpha that was spent at the first interim analysis, thus preserving the overall type I error of the entire trial. Since the purpose of this interim analysis is to fully explore the data to inform the design of a phase III trial, all endpoints, except the fluorescein angiogram endpoints, will be analyzed and a complete set of tables and figures will be produced for the interim as well as for the final analysis. If one or more of the doses of X82 is stopped for any reason, any hypothesis test result from the final analysis regarding those dropped doses will be considered exploratory. The Hochberg procedure described in Section 11.4 will be applied to all 3 doses to preserve the significance level at final analysis for testing of the doses not dropped.

11.8 STATISTICAL METHODOLOGY

The final analysis of this trial will occur after all data from the first 52 Weeks are available. At this time, the data from the first 52 Weeks will be locked and the Sponsor will be unmasked. This section briefly describes the methods to be used to analyze the data. A Statistical Analysis Plan (SAP), to be written prior to unmasking the data, will describe the statistical analysis of the primary, secondary, and other outcomes in detail. Should the methods in the SAP differ from the description in this protocol, the methods in the SAP shall prevail.

11.8.1 Efficacy

The change in mean visual acuity (ETDRS BCVA at 4 m) in the X-82 group compared to the change in mean VA in the placebo group from Day -1 up to and including Week 52 visit will be analyzed using a restricted maximum likelihood (REML)-based repeated measures approach (Malinckrodt 2008).

The analysis will use data from all scheduled post-baseline visits up to and including the outcome visit (52 weeks). The model will include the fixed, categorical effect of treatment visit, as well as the continuous, fixed covariate of baseline visual acuity score and baseline score-by-visit interaction.

An unstructured covariance matrix will first be used to model the within-subject errors, allowing flexibility in the variance and correlation estimates. If there are convergence problems in fitting the model, the following covariance structures will be used until the model converges (in order of decreasing flexibility): heterogeneous Toeplitz, first-order heterogeneous autoregressive, and first-order homogeneous autoregressive.

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The main comparison will be the test for the treatment effect at the endpoint visit (52 weeks) obtained by using an appropriate contrast of the treatment-related model parameters.

The X-82 group will be compared to the placebo group with respect to the number of ivt anti-VEGF injections up to and including week 52 by comparing the means calculated by an analysis of variance.

The secondary efficacy outcome (number of injections per year) will be tested for any dose reaching significance for the primary outcome (visual acuity) at the time of final analysis; the test will use the same significance level for the secondary efficacy outcome as for the primary outcome (e.g. if α=0.04 at the final analysis for the primary efficacy outcome, the secondary efficacy outcome will be tested at α=0.04).

Data from the other efficacy outcomes listed above will be summarized. Statistical analysis of these outcomes will be descriptive, with no correction for multiplicity.

11.8.2 Safety

Safety will be evaluated by assessing the incidence of adverse events (AEs), the incidence of serious adverse events (SAEs).

AEs, SAEs, and other findings will be summarized by presenting the percentages of subjects with each event for each treatment group. When relevant, the time course of adverse events will be presented.

12 SAFETY REPORTING

Safety Analysis

The safety of X-82 will be assessed through the collection and analysis of AEs, baseline medical conditions, results of the review of body systems, vital signs, complete ocular examination, and laboratory tests. Other protocol-specified tests that are deemed critical to the safety evaluation of the X-82 will be used to evaluate safety. All safety assessments, including occurrence of AEs, intensity/severity, relationship to study drug, and treatment or action taken to resolve the event, will be performed by the evaluating physician.

12.1 DEFINITIONS OF ADVERSE EVENTS

An AE is any untoward, undesired, or unplanned event in the form of signs, symptoms, disease or laboratory or physiologic observations occurring in a person given a study drug or participating in a clinical study. The event does not need to be causally related to the study drug. An AE includes, but is not limited to, the following:

Any clinically significant worsening of a pre-existing condition.

An AE occurring from overdose (i.e. a dose higher than that indicated in the protocol) of a study drug, whether accidental or intentional.

An AE that has been associated with the discontinuation of the use of a study drug.

In order for the Sponsor to collect additional information about the clinically important laboratory or diagnostic tests (eg, blood, urinalysis, ECG) abnormalities, at a minimum, the following abnormalities should be captured on the AE CRF:

- Any test result that meets the criteria for a serious adverse event (SAE).
- Any test abnormality that suggests a disease and/or organ toxicity that is new or has significantly worsened.

- Any test abnormality that required the subject to have study medication discontinued or interrupted.
- Any test abnormality that required the subject to receive specific corrective therapy, close observation, more frequent follow-up assessment, or further diagnostic investigation.

Only clinically significant test abnormalities should be reported as AEs. Determination of the clinical significance of test abnormalities is the responsibility of the Investigator. In particular, mild hematology and chemistry abnormalities should be carefully considered for clinical relevance by the Investigator, as they are less likely to be of clinical significance as compared to moderate or severe abnormalities. A clinical diagnosis, rather than the changes in laboratory or other assessment should be recorded on the CRF as appropriate (eg, anemia versus low hemoglobin value, bundle branch block rather than abnormal ECG).

Serious Adverse Events (SAE)

Any adverse experience occurring at any dose that results in any of the following outcomes is classified as an SAE.

- Results in death
- Life threatening (see below for definition)
- Requires subject hospitalization or prolongs subject hospitalization (see below for definition)
- Results in persistent or significant disability/incapacity (see below for definition)
- Results in a congenital anomaly/birth defect in a neonate/infant

Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious AEs when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Life-threatening refers to immediate risk of death as the event occurred per the reporter. A life-threatening experience does not include an experience, had it occurred in a more severe form, might have caused death, but as it actually occurred, did not create an immediate risk of death. For example, an allergic reaction resulting in angioedema of the face would not be life threatening, even though angioedema of the larynx, allergic bronchospasm, or anaphylaxis can be fatal.

Hospitalization is official admission to a hospital. Hospitalization or prolongation of a hospitalization constitutes criteria for an AE to be serious; however, it is not in itself considered a SAE. In the absence of an AE, a hospitalization or prolongation of a hospitalization should not be reported by the PI. This is the case in the following situations:

- The hospitalization or prolongation of hospitalization is part of a routine procedure followed by the center (e.g., stent removal after surgery). This should be recorded in the study file.

- Hospitalization for survey visits or annual physicals falls in the same category.

Disability is defined as a substantial disruption in a person's ability to conduct normal life functions.

A protocol-related adverse event is an AE occurring during a clinical study that is not related to the study drug, but is considered by the investigator or medical monitor to be related to the research conditions. For example, a protocol-related AE may be an untoward event occurring during a washout period or an event related to a medical procedure required by the protocol.

Other Reportable Information. Certain information, while not meeting the above definition of an AE, is reportable to the sponsor as an SAE. This includes:

- A case involving a pregnancy. Information about use in pregnancy encompasses the entire course of pregnancy and delivery and perinatal and neonatal outcomes, even if there were no abnormal findings. If a pregnancy is confirmed, the study drug must be discontinued immediately. All reports of pregnancy must be followed for information about the course of the pregnancy and delivery, as well as the condition of the newborn. When the newborn is healthy, additional follow-up is not needed.

12.2 ADVERSE EVENT RECORDING AND REPORTING

An AE or SAE can occur from the time that the subject signs the informed consent form to 30 days from the subject's last dose, regardless of study drug or protocol relationship. After 30 days, only AEs or SAEs determined by the investigator to be related to study drug are to be reported. All adverse events, regardless of severity and whether or not they are ascribed to the study treatment, will be recorded in the source documents. All AEs and SAEs for subjects who are not screen failures will be recorded on the CRFs.

The investigator must follow-up on all AEs, SAEs, and other reportable events until the events have subsided, returned to baseline, or in case of permanent impairment, until the condition stabilizes. If, in the opinion of the investigator, the AE or laboratory abnormality/ies are not likely to improve because of the underlying disease, the investigator must record his or her reasoning for this decision in the subject's source documentation and as a comment on the CRF. Any medication or other intervention necessary for the treatment of an adverse event must be recorded on the concomitant medication case report form.

All AEs will be characterized by the following criteria:

- Event term
- Intensity or severity
- Expectedness
- Relationship to study treatment
- Outcome
- Treatment or action taken.

Whenever possible, recognized medical terms should be used when recording AEs. Colloquialisms and/or abbreviations should not be used.

If more than one distinct adverse event occurs, each event should be recorded separately. However, if known at the time of reporting, a diagnosis (i.e., disease or syndrome) should be recorded on the CRF rather than individual signs and symptoms (e.g., record congestive heart failure rather than dyspnea, rales, and cyanosis). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as a separate AE. A diagnosis that is subsequently established should be reported as follow-up information. However, signs and symptoms that are considered unrelated to an encountered syndrome or disease should be recorded as individual AEs (e.g., if congestive heart failure and severe headache are observed at the same time, each event should be recorded as an individual AE).

Adverse events occurring secondary to other events (e.g., sequelae) should be identified by the primary cause; a "primary" event, if clearly identifiable, should represent the most accurate clinical term to record as the AE event term. For example:

Orthostatic hypotension $\Rightarrow$fainting and fall to floor $\Rightarrow$head trauma $\Rightarrow$neck pain

The primary event is orthostatic hypotension and the sequelae are head trauma and neck pain.

12.2.1 Classification of Adverse Events by Intensity/Severity

All adverse events should be graded on a 3-point scale (mild, moderate, severe) for intensity/severity. These definitions are as follows:

Mild: Transient discomfort; no medical intervention/therapy required and does not interfere with daily activities.

Moderate: Moderate level of discomfort or concern with moderate limitation in daily activities; some assistance may be needed; minimal or no medical intervention/therapy required.

Severe: Extreme discomfort and limitation in daily activities, significant assistance required; significant medical intervention/therapy required.

There is a distinction between the severity and the seriousness of an adverse event. Severity is a measurement of intensity; thus, a severe reaction is not necessarily a serious adverse event (SAE). For example, a headache may be severe in intensity, but would not be serious unless it met one of the criteria for serious adverse events.

12.2.2 Expectedness

All AEs considered related to X-82 will be evaluated as to whether they are expected or unexpected. Expectedness will be determined by the Sponsor.

Expected (anticipated): An adverse event is expected when the nature, severity, or degree of incidence was previously described in the IB.

Unexpected (unanticipated): An adverse event is unexpected when the nature, severity, or degree of incidence was not previously described in the IB.

12.2.3 Relatedness

The study investigator will evaluate if the AE is related to X-82. Relationship is defined in the following manner:

Not related: Evidence indicates no plausible direct relationship to the study drug, such that:

- A clinically plausible temporal sequence is inconsistent with the onset of the AE and drug administration; and/or
- A causal relationship is considered biologically implausible
- The AE can be attributed to concurrent/underlying illness, other drugs, or procedures.

Related: Evidence indicates a reasonable temporal sequence of the event with the study drug administration exists, or that the association of the event with study drug administration is unknown and the event is not reasonably supported by other conditions, such that:

- There is a clinically plausible time sequence between onset of the AE and study treatment administration; and/or
- There is a biologically plausible mechanism for study treatment causing or contributing to the AE; and
- The AE cannot be reasonably attributed to concurrent/underlying illness, other drugs, or procedures.

12.2.4 Outcome

The clinical outcome of an AE will be characterized as follows:

- Resolved without sequelae
- Resolved with sequelae (specify)
- Ongoing (i.e. continuing at time of study discontinuation)
- Death.

12.2.5 Treatment or Action Taken

- None
- Medical Intervention
- Surgical Intervention
- Other.

12.3 SERIOUS ADVERSE EVENT REPORTING

Serious Adverse Events (SAE) must be reported to the study sponsor as soon as possible and no later than 24 hours after the Investigator first learns of the event. The SAE form is to be completed and submitted by email to Tyrogenex. For initial reports, investigators should record all case details that can be gathered within the reporting timeframe. Relevant follow-up information should be submitted to the study sponsor as soon as it becomes available and/or

upon request. For some events, the sponsor or its designee or the medical monitor may follow up with the site by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the event (e.g., hospital discharge summary, consultant report, or autopsy report). Reports relating to the subject's subsequent medical course must be submitted to the study sponsor until the event has resolved or, in case of permanent impairment, until the event stabilizes and the overall clinical outcome has been ascertained.

Pregnancy and symptomatic overdose should be reported following SAE reporting timelines.

The SAE report should be sent to Tyrogenex via e-mail using the using the following contact information (during both business and non-business hours):

SafetyFax@SynteractHCR.com

To speak to the Medical Monitor directly regarding any SAE or medical concern contact:

Medical Monitor:
Dr. Stephan de la Motte
Email: Stephan.delaMotte@syntheracthcr.com
Direct: +49 89 12 66 80 2509

Transmission of the SAE report should be confirmed by the site personnel submitting the report.

Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to the sponsor as soon as it is available; these reports should be submitted using the SAE Report Form.

12.4 UNMASKING

Treatment assignment will be masked to minimize bias in study assessments and monitoring. The randomization list will not be available to the subjects, study sites, or Sponsor until database lock.

The drug supply vendor staff are authorized to receive the randomization list to facilitate drug packaging and monitor the site inventory. The medical monitor will unmask treatment assignment only for individual subjects who have SAEs that are both unexpected and related in order to allow appropriate safety reporting to regulatory authorities.

For emergency unmasking, when knowledge of the treatment assignment will impact the clinical management of the patient, the Investigator or designee will contact the IWRS prior to unmasking a subject. The IWRS will then provide the site with the subject's unmasking code and the subject must be discontinued from study treatment. Whenever possible the Investigator is encouraged to contact the Sponsor or Medical Monitor prior to unmasking any subject's treatment assignment.

13 STUDY COMPLETION

13.1 SUBJECT DISCONTINUATION

Subject participation is voluntary; any subject may discontinue participation in the study without prejudice or may be withdrawn from the study by the Investigator or Sponsor for the following reasons:

- Pregnancy
- Intolerable toxicity thought to be related
- Patient request
- Inability to comply with trial requirements
- Conditions requiring treatment intervention not permitted by protocol
- Intercurrent illness (investigators discretion)
- Non-compliance/lost to follow-up
- Discontinuation by Sponsor

If the subject wishes to withdraw study consent, every effort will be made to encourage the subject to return to the study site for a final visit prior to withdrawing consent.

13.2 LOST TO FOLLOW UP

The study sites will attempt to follow-up on subjects who do not return for scheduled study examinations. Sites must make a minimum of three documented attempts via telephone, email, or regular mail to contact the subject. If the subject does not reply to any of these attempts, the site must send a letter by certified mail (with a request for notification of receipt of delivery) to the subject. If a subject is non-responsive to these follow-up attempts, he/she will be considered to be lost to follow-up and the CRF will be updated to note lost to follow-up as the reason for discontinuation.

13.3 EARLY SUBJECT TERMINATION / SUBJECT WITHDRAWAL

Subjects who discontinue treatment early for any reason will be asked to undergo Week 52 assessments. These subjects will be followed for up to 30 days after the last dose of study medication for the development of new AEs.

13.4 FOLLOW-UP OF SUBJECTS WITH ADVERSE EVENTS

If any study subject has an adverse event at the time of completion, termination or withdrawal, the subject should be followed until resolution or stabilization of the adverse event. If in the opinion of the investigator, the AE or laboratory abnormality/ies are not likely to improve because of the underlying disease, the investigator must record his or her reasoning for this decision in the subject's medical record and as a comment on the CRF.

13.5 STUDY SUSPENSION, TERMINATION AND COMPLETION

The Sponsor may suspend or terminate the study at any time for any reason.

If the investigator suspends or terminates the study, the investigator will promptly inform the Sponsor and the IRB and provide them with a detailed written explanation. The investigator will also return all study drug and other materials to the Sponsor. Upon study completion, the investigator will provide the IRB with notice of closure.

14 ETHICAL AND REGULATORY CONSIDERATIONS

14.1 COMPLIANCE STATEMENT, ETHICS AND REGULATORY COMPLIANCE

This study will be conducted in compliance with the protocol, principles set forth in the Declaration of Helsinki (1998 version applicable for study sites in the EU), International Conference on Harmonization (ICH) Guideline E6 for Good Clinical Practice (GCP) (CPMP/ICH/135/95 Jan 1997), and the U.S. Code of Federal Regulations (CFR) Title 21, parts 50, 54 56, and 312.

14.2 IRB APPROVAL

The study protocol, subject information and consent form, the Investigator Brochure, any subject diary card or written instructions to be given to the subject, available safety information, subject recruitment procedures (e.g., advertisements), information about payments and compensation available to the subjects and documentation evidencing the Investigator's qualifications should be submitted to the IRB for ethical review and approval according to local regulations, prior to the study start. The written approval should identify all documents reviewed by name and version.

Changes in the conduct of the study or planned analysis will be documented in a protocol amendment. The Investigator must submit and, where necessary, obtain approval from the IRB and/or Sponsor for all subsequent protocol amendments and changes to the informed consent document or changes of the investigational site, facilities or personnel. The Investigator should notify the IRB of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from the Sponsor in accordance with local procedures.

Safety updates for X-82 will be prepared by the Sponsor or its representative as required, for submission to the relevant IRB.

14.3 INFORMED CONSENT

Informed consent is a process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

The informed consent form will be submitted for approval to the IRB that is responsible for review and approval of the study. Each consent form must include all of the relevant elements currently required by the national regulatory body, as well as local county authority or state regulations.

Before recruitment and enrollment into the trial, each prospective candidate will be given a full explanation of the trial. Once the essential information has been provided to the prospective candidate, and the investigator is sure that the individual candidate understands the implications of participating in this trial, the candidate will be asked to give consent to participate in the trial by signing an informed consent form. A notation that written informed consent has been obtained will be made in the subject's medical record. A copy of the informed consent form, to include the subject's signature, will be provided by the investigator to the subject.

If an amendment to the protocol substantially alters the trial design or the potential risks to the subjects, the subject's consent to continue participation in the trial should be obtained.

14.4 SUBJECT CONFIDENTIALITY

Confidentiality of subject's personal data will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and national data protection laws, as applicable. HIPAA regulations require that, in order to participate in the trial, a subject must sign an authorization from the trial that he or she has been informed of following:

- What protected health information (PHI) will be collected from subjects in this trial;
- Who will have access to that information and why;
- Who will use or disclose that information;
- That health information may be further disclosed by the recipients of the information, and that if the information is disclosed the information may no longer be protected by federal or state privacy laws;
- The information collected about the research trial will be kept separate from the subject's medical records, but the subject will be able to obtain the research records after the conclusion of the trial;
- Whether the authorization contains an expiration date; and
- The rights of a research subject to revoke his or her authorization.

In the event that a subject revokes authorization to collect or use his or her PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the subject is alive) at the end of their scheduled trial period.

In compliance with ICH GCP guidelines, it is a requirement that the investigator and institution permit authorised representatives of Sponsor, the regulatory authorities and the IRB direct access to review the subject's original medical records at the site for verification of trial-related procedures and data.

Measures to protect confidentiality include: only a unique trial number and initials will identify subjects on the CRF or other documents submitted to the Sponsor. This information, together with the subject's date of birth, will be used in the database for subject identification. Subject names or addresses will not be entered in the CRF or database. No material bearing a subject's name will be kept on file by the Sponsor. Subjects will be informed of their rights within the ICF.

15 RECORD KEEPING AND RETENTION

15.1 AMENDMENTS TO THE PROTOCOL

Amendments to the protocol shall be planned, documented and signature authorized prior to implementation.

If an amendment to the protocol is required, the amendment will be originated and documented by the Sponsor (or its representative). The written amendment must be reviewed and approved by the Sponsor, and submitted to the IRB for approval.

Amendments specifically involving change to trial design, risk to subject, increase to dosing or exposure, subject number increase, addition or removal of new tests or procedures, shall be reviewed and approved by the appropriate IRB.

The amendment will be submitted formally to regulatory authorities by the Sponsor as applicable, after IRB approval and specifically when an increase to dosing or subject exposure and/or subject number has been proposed; or, when the addition or removal of an Investigator is necessitated.

15.2 DOCUMENTATION REQUIRED TO INITIATE THE STUDY

The Investigator must provide the Sponsor or its designee with the following documents prior to study initiation and retain a copy in the study file:

- A completed and signed Form FDA 1572. If during the course of the study any changes occur that are not reflected on the 1572, a new 1572 form must be completed and returned to Sponsor/CRO for submission to the FDA.
- Current curriculum vitae and medical licenses (within 2 years) for the Principal Investigator.
- A copy of the original approval for conducting the study by the IRB. Renewals, with continuance of the study, must be submitted at yearly intervals or as required by IRB policy.
- A copy of the IRB approved informed consent form.
- The signature page of this protocol signed and dated by the Principal Investigator.

In addition to the documents listed above, the study site will also retain the following items:

- Certifications and laboratory reference ranges for the central laboratory used for this study.
- All original informed consent forms with required signatures
- All IRB correspondence (i.e., informed consent [including any approved revisions], protocol, AE, advertisements, newsletters)

- Clinical and non-clinical supply shipment forms
- Copies of all correspondence pertaining to the study between the Sponsor or its designee and the site
- Copies of all SAE reports submitted to the Sponsor or its designee
- Study personnel signature log.

15.3 STUDY DOCUMENTATION AND STORAGE

All study-related records must be maintained for at least 2 years after a marketing application is approved for the drug; or if an application is not approved for the drug, until at least 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA/health authorities or regulatory agencies have been notified. The Sponsor will notify the principal investigator when records are no longer needed. The investigator will not discard any records without notifying the Sponsor. If the principal investigator moves from the current investigational site, the Sponsor should be notified of the name of the person who will assume responsibility for maintenance of the records at the investigational site or the new address at which the records will be stored. The investigator will notify the Sponsor as soon as possible in the event of accidental loss or destruction of any study documentation

15.4 DATA COLLECTION

The electronic CRF (eCRF) is the primary data collection instrument for the trial. eCRFs will be kept current to enable the monitor to review the subjects' status throughout the course of the trial. In order to maintain confidentiality, only the study number, subject number and date of birth will identify the subject in the eCRF. All data requested on the eCRF must be supported by and be consistent with the subject's source documentation.

Source documents are the original documents, data, records and certified copies of original records of clinical findings, observations and activities from which the subject's eCRF data are obtained. These can include, but are not limited to, hospital records, clinical and office charts, laboratory, medico-technical department and pharmacy records, diaries, microfiches, ECG traces, copies or transcriptions certified after verification as being accurate and complete, photographic negatives, microfilm or magnetic media, X-rays, and correspondence.

All missing data must be explained. When a required laboratory test, assessment, or evaluation has not been done or an "Unknown" box is not an option on the eCRF, a note should be created verifying that the field was "Not Done" or "Unknown". For any entry errors made, the error(s) must be corrected, and a note explaining the reason for change should be provided.

The investigator will sign and date the subject eCRF casebook indicating that the data in the eCRF has been assessed. Each completed eCRF will be electronically signed and dated by the PI, once all data for that subject is final.

15.5 STUDY MONITORING, AUDITING, AND INSPECTING

The investigator will permit monitoring, quality audits, and inspections by the government regulatory authorities, and the Sponsor or its representative(s) of all study related documents (e.g., source documents, regulatory documents, data collection instruments, case report forms).

Study monitoring involves the following elements:

- Tyrogenex personnel, or designee, may meet with investigators prior to the initiation of the study in order to review the adequacy of the subject population, facilities, and equipment with respect to the needs of the study, and to familiarize the investigator and support staff with the study protocol.

- Tyrogenex personnel, or designee, may meet with the investigators at the time enrollment is initiated in order to ensure that subjects are being properly selected, that the methods described in the study protocol are thoroughly understood by the investigator, and that study data are being correctly recorded.

- Tyrogenex personnel, or designee, may visit the clinical site at any time during the course of the study to review and/or collect completed case report forms. Additionally, telephone consultation will occur as necessary during the course of the study to ensure the proper progress and documentation of the study findings.

15.6 DISCLOSURE AND PUBLICATION POLICY

All information provided regarding the trial, as well as all information collected/documented during the course of the trial, will be regarded as confidential. The Sponsor reserves the right to release literature publications based on the results of the trial. Results from the trial will be published/presented as per the Sponsor's publication strategy.

Inclusion of the investigator in the authorship of any multi-center publication will be based upon substantial contribution to the design, analysis, interpretation of data, drafting and/or critically revising any manuscript(s) derived from the trial. The investigator acknowledges that the trial is part of a multi-center trial and agrees that any publication by the investigator of the results of the trial conducted at his/her research site shall not be made before the first multi-center publication. In the event there is no multi-center publication within fifteen (15) months after the trial has been completed or terminated at all trial sites, and all data has been received, the investigator shall have the right to publish its results from the trial, subject to the notice requirements described herein and subject to acknowledgement of the Sponsor as appropriate. Investigator shall provide the Sponsor thirty (30) days to review a manuscript or any poster presentation, abstract or other written or oral material which describes the results of the trial for the purpose only of determining if any confidential or patentable information is disclosed thereby. If the Sponsor requests in writing, the investigator shall withhold any publication or presentation an additional sixty (60) days solely to permit the Sponsor to seek patent protection.

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APPENDIX 1 SCHEDULE OF ASSESSMENTS

Assessment	Screening Visit 1	Screening Visit 2	Day -1	Weeks 4 to 48	Week 52	1 Month Post-Treatment Follow-up	Early Termination
Visit Window	**Day -29**	**Day -14 (-7/+7)**	**Day -1 (+3)**	**±7 days**	**±7 days**	**±7 days**	
Informed Consent	**X**[3]						
Randomization			**X**				
Demographics	**X**						
Med History/Con Meds	**X**						
Ophthalmic History	**X**						
Vital Signs		**X**		**X**	**X**	**X**	**X**
Height and Weight		**X**			**X***		**X***
Labs and urinalysis		**X**		**X**	**X**	**X**	**X**
Pharmacokinetic Sampling				**X**[1]			
Pharmacogenetic Sampling					**X**		**X**
ECG		**X**		**X**[2]	**X**		**X**
Urine Pregnancy Test		**X**					
Ophthalmic Exam		**X**	**X**	**X**	**X**	**X**	**X**
IOP		**X**	**X**	**X**	**X**	**X**	**X**
ETDRS Visual Acuity		**X**	**X**	**X**	**X**	**X**	**X**
Study Medication Dispensed & Review of Dispensing Log			**X**	**X**			
FA & Photos (sent to IRC)		**X**			**X**		**X**
SD-OCT (sent to IRC)	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Mandatory Anti-VEGF injection	**X**		**X**				
Anti-VEGF injection if required (*prn*)				**X**	**X**	**X****	**X**
AEs/ConMed changes	**X**	**X**	**X**	**X**	**X**	**X**	**X**

** Anti-VEGF therapy after week 52 will be standard of care for each ophthalmology practice

* weight only

[1] Week 4, ***and*** Week 16 ***or*** Week 20, ***and*** Week 40, 44 ***or*** Week 48 only

[2] Week 4 12, 20, 28, 36, and 44

[3] Consent obtained from patients prior to any pre-screening which results in the change of the patients' standard of care or management

APPENDIX 2
DRUGS WITH A KNOWN RISK OF TORSADES DE POINTES AND/OR THAT PROLONG QT INTERVAL SHOULD BE USED WITH CAUTION.

This is not a comprehensive list. A complete list of drugs with a known risk of TdP may be found and is updated at the following web address: qtdrugs.org/medical-pros/drug-lists/drug-lists.htm

Anesthetic
Propofol (Diprivan®, Propoven®)
Sevoflurane (Ulane®, Sojourn®)
Cocaine (Cocaine)

Antiarrhythmics
Amiodarone (Cordarone®) (Pacerone®)
Disopyramide (Norpace®)
Dofetilide (Tikosyn®)
Ibutilide (Corvert®)
Procainamide (Pronestyl®) (Procan®)
Quinidine (Quinaglute®) (Cardioquin®)
Sotalol (Betapace®)
Dronedarone (Multaq)
Flecainide (Tambocor), (Almartym), (Apocard), (Ecrinal), (Flecaine)

Antibiotics
Azithromycin (Zithromax®, Zmax®)
Ciprofloxacin (Cipro ®),(Cipro-XR®), (Neofloxin®)
Levofloxacin (Levaquin), (Tavanic)
Clarithromycin (Biaxin®)
Erythromycin (Erythrocin®) (E.E.S. ®)
Gatifloxacin (ocular drops permitted)
Moxifloxacin
Sparfloxacin (Zagam®)

Antihistamines
Astemizole (Hismanal)
Terfenadine (Seldane)

Antipsychotics
Chlorpromazine (Thorazine®)

Haloperidol (Haldol®)
Levomepromazine (Nosinan), (Nozinan), (Levoprome)
Levomethadyl (Orlaam)
Droperiodol (Inapsine®, Droleptan®, Dridol®, Xomolix®)
Mesoridazine (Serentil®)
Pimozide (Orap®)
Risperidone (Risperdal®)
Thioridazine (Mellaril®)
Ziprasidone

Antidepressants
Citalopram (Celexa®, Cipramil®)
Escitalopram (Cipralex®, Lexapro®, Nexito®, Seroplex®, Elicea®, Lexamil®, Lexam®)

Antifungals (azoles)
Fluconazole (Diflucan®, Trican®)
Pentamidine (Pentam®) (NebuPent®)

Antimalarials
Chloroquine (Arelan®)
Halofantrine (Halfan®)

Antiemetics
Ondansetron (Zophran®)
Domperidone (Motilium®, Motillium®, Motinorm Costi®, Nomit®)

Miscellaneous
Arsenic trioxide (Trisenox®)
Anagrelide (Agrylin), (Xagrid)
Bepridil (Vascor®)
Methadone (Dolophine), (Symoron), (Amidone), (Methadose), (Physeptone), (Hepadon)
Cisapride (Propulsid®)
Cilostazol (Pletal)
Donepezil (Aricept®)
Bepredil (Vasocor)
Probucol (Lorelco)

APPENDIX 3
COMMON P450 INHIBITORS, INDUCERS AND SUBSTRATES

The following tables from the FDA Drugs website describe medications and foods which are common inhibitors, inducers and substrates of P450, including CYP3A. Potent (i.e., strong or moderate) CYP3A4 inhibitors or inducers should be avoided during this study. This list should not be considered all-inclusive. Consult individual drug labels for specific information on a compound's propensity to interact with these enzymes.

From FDA Drugs Website- inclusion of relevant CYP isozymes and categories

Drug Development and Drug Interactions:
Table of Substrates, Inhibitors and Inducers

Classification of Inhibitors

Table 5. Classification of In Vivo Inhibitors of CYP Enzymes [1] (7/28/2011)
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

CYP Enzymes	Strong Inhibitors[2] ≥ 5-fold increase in AUC or > 80% decrease in CL	Moderate inhibitors[3] ≥ 2 but < 5-fold increase in AUC or 50-80% decrease in CL
CYP3A	Boceprevir, clarithromycin, conivaptan, grapefruit juice,[11] indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil,[12] nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	Amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice,[11] imatinib, verapamil

1. Please note the following: This is not an exhaustive list. For an updated list, see the following link:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

2. A strong inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a substrate for that CYP by equal or more than 5-fold.
3. A moderate inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 5-fold but equal to or more than 2-fold.

11. The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (e.g., high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (e.g., low dose, single strength).
12. Withdrawn from the United States market because of safety reasons.

Table 6. Classification of In Vivo Inducers of CYP Enzymes[1] (7/28/2011)

CYP Enzymes	Strong Inducers ≥ 80% decrease in AUC	Moderate Inducers 50-80% decrease in AUC
CYP3A	Avasimibe,[5] carbamazepine, phenytoin, rifampin, St. John's wort[3]	Bosentan, efavirenz, etravirine, modafinil, nafcillin

(1) Please note the following: This is not an exhaustive list. For an updated list, see the following link:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm
(3) The effect of St. John's wort varies widely and is preparation-dependent.
(5) Not a marketed drug.

APPENDIX 4
SPONSOR'S COMMITMENTS

The Sponsor is committed to:

1. Complying with all applicable health authority regulations governing the conduct of clinical research studies, including the U.S. Food and Drug Administration.
2. Protecting the rights, health, safety and welfare of study subjects.
3. Informing the clinical investigators of any new information about the study which may affect the health, safety or welfare of the subjects, or may influence their decision to continue participation in the study.
4. Providing the clinical investigators with the study protocol, and access to electronic Case Report Forms on which to document the study evaluation variables for each subject entered into the study.
5. Providing the statistical analysis and study report writing resources necessary to complete reporting of the study results.
6. Ensuring equity of consideration among all investigators in multicenter studies in all matters of publications, meeting presentations, etc.
7. Certifying that IRB/EC approval of the protocol and Investigators Agreement will be completed prior to treatment at an investigational site.

APPENDIX 5
INVESTIGATOR'S QUALIFICATIONS AND RESPONSIBILITIES

Each Investigator must be a licensed physician who has completed a residency or preceptorship in ophthalmology. The Investigators have the following responsibilities:

1. Subject Selection

The Investigator is responsible for assuring that all subjects entering the study conform to the patient selection criteria.

2. Informed Consent

The Investigator is responsible for fully reviewing the nature of the study, the possible risks, and alternative treatments with prospective patients prior to their enrollment in the study. The Investigator is responsible for obtaining written Informed Consent in compliance with 21 CFR 50 for each patient, prior to enrollment in the trial. A copy of the signed Informed Consent Form will be maintained in the patient's medical record.

3. Institutional Review Board (IRB) Approval

The Investigator must obtain approval for his participation in this protocol from the IRB/EC for the institution at which the procedure will be performed, prior to entering any patients in the study. The Informed Consent document to be used will also be submitted by the Investigator to the IRB/EC for approval prior to initiation of the study. Assurance that the IRB/EC approval of the study protocol and Informed Consent has been obtained will be provided to the Sponsor prior to initiation of the study.

4. Subject Evaluations and Data Reporting

The Investigator is responsible for complying with the requirements of the study protocol, any amendment or clarifications as published by the study Sponsor (Tyrogenex) and performing the patient evaluations as described in the study protocol. All information generated by the patient evaluation will be recorded using CRFs with access provided by the Sponsor. Original laboratory reports will be retained by the Investigator, but as the results become available, they will be entered on appropriate CRFs.

Investigator(s) will not deviate from the study protocol without prior approval of Tyrogenex unless protection of the health, safety or welfare of study subjects requires prompt action.

5. Record Retention

The Investigator shall maintain all patient records for whichever of the following periods is shortest:

a. A period of two years after the date on which the FDA approves the marketing of the drug for the purpose that was the subject of the study.
b. A period of five years after the date on which the results of the study are submitted to the FDA in support of the marketing of the drug for the purpose that was the subject of the study.

6. Investigational Material Accountability

The Investigator must maintain accurate records of the receipt of all investigational material shipped by Tyrogenex, including the date, and identification numbers of the product received. In addition, accurate records must be kept on the amount and date that investigational material, by identification number, was dispensed or returned to the Sponsor. The Investigator must assure that study supplies be dispensed only to subjects enrolled in the study per the inclusion / exclusion criteria and under the direct supervision of the Investigator or his / her sub-investigators.

Records of all investigational supplies received, used and returned must be kept by the Investigator. All unused investigational supplies will be returned to the Sponsor as soon as practical upon completion of the trial. Investigational material accounting procedures must be completed before the study is considered terminated.

APPENDIX 6
DECLARATION OF HELSINKI

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington, DC, USA, October 2002
(Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo, Japan, October 2004
(Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, Korea, October 2008

A. INTRODUCTION

1 The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.
The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2 Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3 It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

4 The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

5 Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6 In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7 The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8 In medical practice and in medical research, most interventions involve risks and burdens.

9 Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10 Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.
17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.
20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.
26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.
30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the

physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

    - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
    - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

APPENDIX 7 ASSESSMENT OF VISUAL ACUITY

Refraction and visual acuity (VA) measurements will be performed for all patients by trained vision examiners only. The **name and certification number** of the vision examiner should be documented in the patient's **source document** at each visit. VA examiners are "masked" to trial assignment and where possible to the previous VA testing results. Instead only the previous refraction should be made available. Refraction should be conducted prior to VA testing to obtain best-corrected vision as described below. Best-corrected visual acuity (BCVA) is measured at all trial visits using standard charts, lighting, and procedures. Best correction is determined by careful refraction at that visit according to the standard protocol for refraction as described below.

Equipment

Refraction equipment required includes:

1. Retroilluminated Light box and ETDRS 4 meter distance acuity chart set
2. Trial lens frames
3. Trial lens set with plus or minus cylinder lenses
4. Jackson cross-cylinders of 0.25, 0.50, and 1.00 diopters
5. Pinhole occluder
6. Tissues or eye pads and tape
7. A 1 meter rigid measuring stick

Visual Acuity Charts

Chart 1 is used for testing the VA of the RIGHT eye; Chart 2 for testing the LEFT eye; and Chart R (or 3) for refraction only. Patients should not be allowed to see any of the charts before the examination.

Visual Acuity Lane and Visual Acuity Box

A distance of **4 meters** is required between the patient's eyes and the VA chart. With the box light off, not more than **15 foot-candles of light** (161.4 Lux) should fall on the center of the chart. To measure the amount of light, the room is set up for VA testing, but with the box light off. The light meter is placed at the fourth line from the top of the chart, with its back against the chart and the reading is taken. If more than one lane is available for testing VA, the VA of an individual patient should be measured in the same lane at each visit, if possible. If different lanes are used to test VA, they must each meet the same standards.

Retro illuminated ETDRS charts are used in this trial. The illuminator box will be either wall-mounted or mounted on a stand. The light box should be mounted at a height such that top of third row letter is 49 ± 2 inches from floor.

The VA light box is equipped with two General Electric 20-watt fluorescent tubes and ballast. Each tube is partly covered by a 14-inch fenestrated sleeve, which is centered on the tube and open in the back. This serves as a "baffle" to produce even illumination over the testing chart. Because the illumination of fluorescent tubes diminishes by 5 percent during the first 100 hours and by another 5 percent during the next 2000 hours, new tubes should be kept on for 4 days (96 hours) continuously, and should be replaced once a year.

A **sticker** should be placed on the back of the light box, indicating the date on which the present tubes were installed. A spare set of burned in bulbs should be available on site.

Beginning Approximate Refraction

At the Baseline visit, the patient's beginning refraction is determined by one of the following ways:

If the patient's VA is 6/30 (20/100) or better and the patient does not require glasses for distance vision, then the beginning approximate refraction should be no lens correction or plano.

If the patient's VA is 6/30 (20/100) or better and the patient requires glasses for distance viewing, the glasses should be measured using a focimeter, and these measurements are used for the beginning refraction.

If the patient's VA is less than 6/30 (20/100) with or without correction, then retinoscopy, or auto refraction should be performed to determine the beginning approximate refraction.

If the patient wears contact lenses for refraction, a notation should be made that the refraction was over contact lenses. It is suggested that the patient wear the contact lenses for future examinations. If the patient is not a regular contact lens wearer and wore the lenses by mistake, they should be removed and you should wait at least 30 minutes before beginning the refraction. The patient should be reminded not to wear contact lenses at subsequent visits.

Refractions are performed with either plus or minus cylinder power. Whichever cylinder type is used at baseline (minus or plus) must be used for all subsequent visits. Best correction results should be recorded on the sponsor provided worksheet which will be included in the source documents. At each **follow-up visit**, **the results of the protocol refraction from the previous visit are used as the beginning approximate refraction**. If the previous refraction is not available for some reason, the procedure described immediately above should be used. Whilst previous refraction results are made available at subsequent visits, **previous VA results should not be visible to the examiners at subsequent testing, so that assessment of VA is masked to prior visual function.**

The charts used for measuring distance VA must NOT be used for refraction. Refraction for each eye should be performed at **4 meters** unless the patient's VA measured at 4 meters on the refraction chart (Chart R or Chart 3) is **worse than 6/48 (20/160)**.**If VA is worse than 6/48 (20/160) the eye is refracted at 1.0 meter**. If during the refraction process at one meter, the patient is reading letters on the eighth line or lower line of the chart, the refraction should continue at 4 meters. Whenever a patient cannot read any letters on the top line of Chart R or Chart 3 at 1.0 meter the vision should be checked with a pinhole to see whether reduced vision is due, at least in part, to a larger refractive error. If there is no improvement with the pinhole, then the eye is exempt from refraction.

Patient Refraction

Patient refraction allows one to determine the best correction for a patient to perform the VA tests. The **"push plus"** approach is used. Add minus diopter spherical corrections **only when the patient is able to read at least one more letter** on a line or a letter on a smaller line.

Procedure

1. Measure and record the distance vision of the eye being tested using Chart R while occluding the fellow eye. The fellow eye should be lightly patched with an eye pad or tissue and tape. Patients should be reminded to blink and encouraged to use eccentric fixation, or their side vision, when necessary.
2. All refraction and vision testing must be done at 4 meters or 1 meter. Distance for 4 meters is 13 feet and 1.5 inches or 157.5 inches. The one meter distance is 39 and 3/8 inches.
3. All patients should be seated for testing. A **rigid measuring device** should be used to measure the distance from the patient to the chart if testing is done at **1 meter**. The distance is measured from the outer canthus to the center of the

second letter (left eye) or fourth letter (right eye) of the third line of the chart. For **4 meter** testing, **clear and permanent floor markings** should be used to mark the distance for consistency.

4. Place and adjust the trial frame on the patient's face so that the lens cells are parallel to the anterior plane of the orbits and centered in front of the pupils. Adjust the lens cells for the proper distance from the cornea. Be sure the trial frame is comfortable on the patient's face.
5. Occlude the left eye by lightly patching with an eye pad or tissue and tape.
   1. Place the spherical lens correction in the compartment closest to the eye.

   The cylindrical lens correction, if present, is placed in the compartment in front of the spherical correction. Adjust the axis.

6. **Spherical Correction:** To determine the highest plus or least minus sphere, refract the right eye. The following refraction steps are recommended for VAs of 6/3 (20/10) to 6/24 (20/80) with the beginning approximate refraction. For VAs less than 6/24 (20/80), refer to the refraction table for the appropriate sphere and cylinder powers and testing distance (See summary below) and follow a similar procedure. *Note: Whenever VA is improved to a higher range, refraction should be performed with the smaller sphere and cylinder powers given for the better VA level (See table at end of appendix).*
   a) Hold a **+0.50 sphere** in front of the patient's right eye. The patient should be looking at the smallest legible line on the VA chart. In these exact words, ask the patient, **"Is this better, worse, or no change?"**
   b) If the patient responds that the vision is **worse or blurred**, remove the +0.50 sphere from in front of the trial frame and **go to Step 6d**.
   c) If the patient responds **better or no change**, remove the +0.50 sphere from in front of the trial frame and replace the spherical lens in the trial frame with a spherical lens that is one-half diopter more positive .Continue this procedure by returning to Step 6a and repeating this process **until a +0.50 makes the vision worse** or blurred and then go to Step 6d.
   d) Hold a **-0.50 sphere** in front of the patient's right eye. In these exact words, ask the patient, "Is this better, worse or no change? "If the patient replies "worse" or "no change", go to Step 6f.If they reply "better" go to step 6e.
   e) Hold the -0.50 sphere in front of the eye. If the patient responds that the vision is better, ask the patient to read the VA chart. **Only when the VA is improved, by at least one letter**, **may you increase the minus** by 0.50 (or decrease the plus) and repeat Step 6d.Whenever VA is not improved, go to Step 6f.
   f) Remove the -0.50 sphere from in front of the eye and hold a +0.50 sphere in front of the right eye. In these exact words, ask the patient, "Is this better, worse, or no change? "If the patient responds that vision is better or

unchanged, then return to Step 6c.Otherwise, go to Step 7. **Spherical testing should always end with a plus lens.**

7. **Cylinder Axis:** To determine and refine the cylinder axis for **PLUS** cylinder, proceed as follows; *(If **minus** cylinders are used, the appropriate technique using minus cylinders must be employed and minus cylinder must be used throughout the trial.)*
   a) Have the patient look at a line which is either **one or two lines larger** than the smallest line the patient is able to read. Ask the patient to focus on a rounded letter such as "C", "D", or "O". The patient should focus on this same letter throughout this procedure.
   b) If a cylinder is present in the beginning approximate refraction, then go to Step 7c. Otherwise, follow the option listed below to determine if cylinder may be needed.

      Testing for cylinder when there is none in the beginning approximate refraction:

      Place a **+0.50 diopter** cylinder with the positive axis first at 90°, then compare this to no cylinder; repeat this procedure for 180°, then 45°, and 135° always comparing to no cylinder after each axis position. If the patient says that vision is improved at any one of the four axis positions, place a +0.50 cylindrical lens in the trial frame at the preferred axis and go to step 7c.If the patient prefers no cylinder at all four axis positions, then go to Step 9.

   c) Place the +0.25 diopter hand held cross-cylinder (for VA 6/3 – 6/24; 20/10-20/80) first with the positive axis 45° to the right of the preferred cylinder axis (as determined above), and second with the positive axis 45° to the left of the preferred cylinder axis. Ask the patient, "Which do you like better, position one or position two?" Also, tell the patient that both positions may blur their vision. The patient must choose the least blurred position, either one or two. "Neither" is allowed only if both positions are equally blurred or equally good.
   d) If "neither" position is better and this was the first test of axis position, move the axis of the cylinder in the trial frame 15° to the right or left and return to Step 7c.Otherwise, proceed to Step 7e.
   e) When one position is preferred over another, move the cylinder to the preferred positive axis position in the step sizes noted below and return to Step 7c.If no single position is better than another than go to Step 8.

Cylinder Refinement *suggested* axis step sizes

Cylinder	Axis Step Sizes

Power	
<1.00D	15º
1.00 to <2.00D	10 º
2.00 to <3.00D	5 º
3.00 to<5.00D	3 º
5.00 to<8.00D	2 º

8. **Cylinder Power**: Cylinder power is refined by following the steps:
   a) Ask the patient to look at the **smallest line** that can be read on the VA chart.
   b) Test the cylinder power by placing the 0.25 diopter cross-cylinder (for vision of 6/3 - 6/24; 20/10-20/80) first with the positive axis and second with the negative axis coincident with the cylinder axis. Ask the patient, "Which is better, position one or position two?" Do not give the patient the choice of neither.
   c) If the patient prefers the minus axis coincident with the cylinder axis, the total power of the correcting plus cylinder is reduced by 0.25 diopter. Repeat the process until the patient cannot choose one of the cross cylinder positions over the other. If the patient indicates a change that would introduce negative cylinder power, remove all cylinder power and continue testing for positive cylinder power at an axis 90°away from the previous axis. Otherwise go to Step 8d.
   d) If the patient prefers the plus axis coincident with the cylinder axis, increase the power of the cylinder by 0.25 diopters and return to Step 8b.Otherwise proceed to Step 8e.
   e) When the patient feels that both positions are equally bad or good, and the cylinder power in the trial frame has changed by more than 0.50 diopter, return to Step 7c and re-check the axis if necessary. Otherwise, proceed to Step 9.

   *Note: If the cylinder is changed by more than 0.50 diopter, the **spherical equivalent** should be maintained.(For each 0.50 **plus** CX increase, add –0.25 to the sphere, for each 0.50 **minus** CX increase, add +0.25 to the sphere).*

9. **Spherical Correction *Refinement***: Recheck, or ***"refine"*** the power of the sphere by adding+**0.25 and -0.25** spheres and changing the spherical power by 0.25 diopter increments of the appropriate sign until the patient cannot detect

any improvement in vision. As a reminder, **minus sphere should only be added if the patient can read additional letters** and spherical testing should always begin and end with a plus lens.

10. Record the lens corrections obtained by patient refraction for the right eye on the examination form in the section for VA measurements as the corrections obtained by protocol refraction for the right eye.
11. Repeat the entire process (Steps 1-10) for the left eye and record the refraction result on the VAE worksheet.

Best Corrected Visual Acuity Measures

As a reminder, Charts 1, 2, and R (or 3) are used for testing the right eye, left eye, and refraction, respectively. Patients should not see the charts until the test begins.

The lens correction from the patient refraction should be in the trial frame worn by the patient.

All eyes must be tested at 4 meters first, even if the refraction was performed at 1 meter

The patient should be seated comfortably directly in front of the chart so that the eyes remain at the 4 meter distance. Testing always begins with the right eye. The fellow should be occluded with a folded tissue or eye pad lightly taped over the eye behind the trial frame serves as an effective occluder that allows eccentric fixation without inadvertent use of the covered eye. After testing the right eye, occlusion of the right eye should be done BEFORE Chart 2 is put up for testing the left eye.

The patient is asked to read the letters slowly, approximately one letter per second. The patient should be told that only one chance is given to read each letter, but they may change their mind before moving to the next letter. If the patient is unsure about the identity of the letter, then the patient should be encouraged to guess.

The patient should begin by reading the top line of the chart and continue reading every letter on each smaller line, from left to right on each line. *The patient should be encouraged to continue reading even if making mistakes. Each letter read is counted.* The examiner circles every correct letter read and totals each line and the whole column (0 if no letters are correct) on the data collection form. An X is put through letters read incorrectly. Letters, for which no guess was attempted, are not marked. When a patient reaches a level where he/she cannot guess, the examiner may stop the test provided that the patient has made errors on previous guesses, which is a clear indication that the best VA has been obtained.

When a patient cannot read at least 20 letters on the chart at 4.0 meters, the patient is tested at 1.0 meter. The distance from the patient to the chart should be measured again using the rigid one meter stick. The distance is measured from the outer canthus to the center of the fourth letter (right eye) or the second letter (left eye) of the third line of the chart. The spherical correction in the trial frame

should be changed by adding +0.75 to correct for the closer test distance. The patient may fixate eccentrically or turn or shake his/her head to improve VA. Particular care should be taken to make sure the patient does not move forward when testing at 1 meter. The patient should be reminded to blink.

The examiner should not tell the patient if a letter was identified correctly. The patient may be encouraged by neutral comments, such as "good", "next", and "OK".

The examiner should not stand close to the chart during testing. Attention should be focused on the patient and the data collection form. If the patient has difficulty locating the next line to read, the examiner may go up to the chart and point briefly to the next line to be read, but then must move away from the chart.

When 20 or more letters are read at 4 meters the VA score for that eye is recorded as the number of letters correct plus 30 (refer to the VA worksheet) The patient gets credit for the 30 1M letters even though they did not have to read them. Otherwise, the VA score is the number of letters read correctly at 1.0 meter plus the number, if any, read at 4M.If no letters are read correctly at either 4.0 meters or 1 meter, then the VA score is recorded as 0.

Testing for Count Fingers Vision, Hand Motion Vision and Light Perception/No Light Perception (NLP) Vision

If the patient's VA is so poor that he/she cannot read any chart letters when tested at one meter then the patient's ability to count fingers, detect hand motion, or have light perception should be evaluated.

Testing for Count Fingers Vision

In testing for count fingers vision, the examiner's hand holding 1, 2, or 5 fingers is held steady at a distance of two feet directly in front of the eye being examined. The fellow eye is completely occluded with a patch on the face. A light should be shown directly on the hand from behind the patient. The examiner's fingers should be presented in random order and repeated 5 times. Eccentric fixation, if present, should be encouraged. If the patient correctly identifies three of the five presentations, then count fingers vision is noted. If not, then the patient must be tested for hand motion vision.

Testing for Hand Motion Vision

The examiner's hand with all fingers spread out should be extended two feet directly in front of the eye being examined. The fellow eye should be occluded with a patch on the patient's face. A light should be shone directly on the examiner's hand from behind the patient. The examiner's hand should be moved in an up-and-down direction (vertically) or in a side-to-side direction (horizontally) at a constant

speed of approximately one back and forth presentation per second. The patient is instructed that the examiner's hand will be presented and they will have to respond to the question: "What am I doing with my hand?" This should be repeated five times. Three out of five correct responses indicate that hand motion vision is present. If the patient does not correctly identify three of five presentations, then you must test for light perception.

Testing for Light Perception/No Light Perception Vision

Light perception should be tested with an indirect ophthalmoscope in a darkened room. The fellow eye should be completely patched and also covered by the patient's hand. The indirect ophthalmoscope light should be in focus at 1 meter with the rheostat set at maximum voltage. From that distance the beam should be directed in and out of the patient's eye at least four times, and the patient should be asked to respond when he or she sees the light. If the examiner is convinced that the patient perceives the light, vision should be recorded as "light perception", if not, vision should be recorded as "no light perception".

4M Refraction Protocol Summary							
Refraction Distance	**Check Sphere First**		**Check Cylinder Axis then Power**			**Sphere "Refinement"**	
If VA on "R" chart is between:	**Power (a)**	**Increment**	**Axis (b)**	**Power (c)**	**Increment**	**Power (d)**	**Increment**
6/3 -6/24 20/10 - 20/80 (4 meters)	**+.50 -.50**	**+.50 -.50**	**.25 JCC**	**.25 JCC**	**+.25 -.25**	**+.25 -.25**	**+.25 -.25**
6/30 – 6/48 20/100 - 20/160 (4 meters)	**+1.00 -1.00**	**+1.00 -1.00**	**.50JCC**	**.50 JCC**	**+.50 -.50**	**+.50 -.50**	**+.50 -.50**
6/60 -6/120 20/200 - 20/400 (1 meter)	**+2.00 -2.00**	**+2.00 -2.00**	**1.00 JCC**	**1.00 JCC**	**+1.00 -1.00**	**+1.00 -1.00**	**+1.00 -1.00**
<6/120 <20/400 (1.0 meters) sequence refraction a-d	**+2.00 -2.00**	**+2.00 -2.00**	**No cylinder test required**			**No refinement required**	

APPENDIX 8: AREDS LENS GRADING PROCEDURE

Overview

The AREDS Clinical Lens Grading Procedure is a simple system for grading the presence and severity of nuclear, cortical and posterior subcapsular lens opacities at the slit-lamp. The validity of the grading results is dependent upon careful adherence to the grading procedures by the examiner. The grading procedures listed below should be read before any grading is done.

- General Instructions
  - Dilate pupils to at least 5 mm diameter
  - Use slit lamp with ~10X magnification
  - Use brightest beam intensity
  - Grade nuclear, cortical and PSC opacities using the 8X10 glossy print of the *"AREDS 2008 Clinical Lens Opacity Standard Photographs"* which has been supplied to you
- Nuclear opacity
  - Orient beam at 45° to viewing axis
  - Adjust slit beam to standard parameters: 8 mm height and 0.3 mm width
  - Compare opalescence of nucleus with that in standard photos
- Cortical and PSC opacities
  - Select wide slit beam setting optimum for retro-illumination of lens
  - Visualize lens opacities against red fundus reflex background
  - Count only opacities definitely visible against red reflex
  - Mentally combine all cortical opacities into one contiguous area
  - Compare total opacity area with that in standard photos
- Classify each opacity with scale defined by 3 standard photos
- Select nearest half-step which is
  - Similar to standard or between two standards
  - Obviously less than mildest standard or greater than most severe

AREDS GRADING SCALE

Grade	Description of Opacity
>1	No Opacity or less than Standard 1
1.0	Same as Standard 1
1.5	More than Standard 1 but less than Standard 2
2.0	Same as Standard 2
2.5	More than Standard 2 but less than Standard 3
3.0	Same as Standard 3
>3	More than Standard 3

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