Oral tyrosine kinase inhibitor for neovascular age-related macular degeneration: a phase I dose-escalation study

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KEY POINTS

Question: X-82 is an oral tyrosine kinase inhibitor that blocks the action of vascular endothelial growth factor (VEGF) and platelet derived growth factor, thus might it treat neovascular age-related macular degenetation?

Findings: In this phase 1 dose escalation study of 35 participants, the most common aderse events attributed to oral X-82 were diarrhea (n=6), nausea (n=5), fatigue (n=5) and transaminase elevation (n=4). The 71% of participants who tolerated X-82 and completed 6 months of treatment averaged only 0.68 intravitreous anti-VEGF rescue injections, with 60% requiring none.

Meaning: These results justify further study, and a phase 2 trial recently completed recruitment.

ABSTRACT

Importance: An oral treatment for neovascular age-related macular degeneration (AMD) would be less burdensome than repeated intravitreous injections. X-82 is an oral tyrosine kinase inhibitor active against vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF).

Objective*:* To undertake safety testing of oral X-82, administered for the treatment of neovascular AMD.

Design*:* Phase I, open-label, uncontrolled, dose-escalation study.

Settting: Five US retinal clinics

Participants*:* Thirty-five participants (mean age 76.8; 16 male:19 female) with neovascular AMD, seven of whom were treatment-naïve.

Interventions*:* Participants received oral X-82 for 24 weeks at 50 mg alternate days (n=3), 50 mg daily (n=8), 100 mg alternate days (n=4), 100 mg daily (n=10), 200 mg daily (n=7), and 300 mg daily (n=3), with intravitreous anti-VEGF therapy using predefined retreatment criteria. Every 4 weeks participants underwent best-corrected visual acuity measurement, fundus examination, and spectral-domain optical coherence tomography

Main Outcome Measures*:* The main outcome was adverse events (AEs). Other outcomes included visual acuity, central subfield retinal thickness, and number of anti-VEGF injections.

Results*:* Of 25 participants (71%) who completed the 24 weeks of X-82 treatment, all maintained or improved their visual acuity (mean +3.8 ± 9.6 letters). Fifteen participants (60%) required no anti-VEGF injections (mean 0.68). Mean central subfield thickness reduced by -50 ± 97 microns, with eight participants (all receiving at least 100 mg daily) demonstrating sustained reductions despite no anti-VEGF injections. The most common AEs attributed to X-82 were diarrhea (n=6), nausea (n=5), fatigue (n=5) and transaminase elevation (n=4). A dose relationship to the transaminase elevations was not identified; all normalized when X-82 was discontinued. All but one were asymptomatic. Ten participants withdrew consent or discontinued prematurely; six due to AEs attributed to X-82, comprising of leg cramps (n=2), elevated alanine aminotransferase (n=2), diarrhea (n=1), and nausea/anorexia (n=1).

Conclusions and relevance*:* X-82 can be associated with reversible, elevated liver enzymes hence liver function testing is needed to identify those unsuited to treatment. Although 17% discontinued X-82 due to AEs, those who completed the study had lower than expected anti-VEGF injection rates. Further studies appear justified, with a phase 2 randomized controlled study underway.

Trial registration: ClinicalTrials.gov, NCT01674569

INTRODUCTION

Tyrosine kinase is an enzyme that transfers a phosphate group to the amino acid tyrosine on proteins. In doing so, it can alter the protein's structure and function, and thereby facilitate signal transduction between macromolecules. In the eye, both vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF) bind to cell surface receptors that rely on a tyrosine kinase to propagate signal transduction into the cell.

Many malignancies are caused by aberrant tyrosine kinase function, which initiates unchecked cell proliferation. Consequently, tyrosine kinase inhibitors are used to treat cancer.[1] Sunitinib is one such tyrosine kinase inhibitor, and is licensed for the treatment of metastatic renal cell carcinoma, gastrointestinal stromal tumors and pancreatic neuroendocrine cancers.[2, 3]

Sunitinib is also a potent inhibitor of angiogenesis,[4] with a rabbit model of corneal neovascularization suggesting topical sunitinib is almost three times as effective as bevacizumab.[5]

X-82 is a novel, potent, oral, multi-kinase, VEGF-receptor and PDGF-receptor inhibitor that is structurally similar to sunitinib. X-82 has been designed to have a smaller volume of distribution than sunitinib with limited tissue accumulation, to minimize side effects. Since X-82 inhibits both the VEGF-receptor and PDGF-receptor kinases, it is intended

as an oral treatment of pathologic angiogenesis in diseases such as neovascular age-related macular degeneration (AMD), von Hippel-Lindau disease and solid tumors.

The first human study of X-82 was as a treatment for solid tumors (Moore KN, et al. Annual Meeting of the American Society of Clinical Oncology, June 1-5, 2012, Chicago, IL.). Sixteen patients with colorectal, renal, carcinoid, and other tumors enrolled in a dose-escalation study, with daily doses from 20 mg to 400 mg. Half the patients showed either stable disease, reduced tumor size or complete remission. None experienced Dose Limiting Toxicity (DLT). The most common adverse events (AEs) were fatigue (n=6), nausea (n=4), diarrhea (n=3), hypertension (n=2) and vomiting (n=2). Ongoing oncology studies are exploring doses up to 800 mg daily (ClinicalTrials.gov: NCT02146222).

Oral X-82 was found to inhibit Matrigel-induced choroidal neovascularization in a rat model (Chuang D, el al, A420, 5-9th May 2009, Association for Research in Vision and Ophthalmology [ARVO], Fort Lauderdale, FL). An oxygen-induced ischemic retinopathy mouse model also showed potent inhibition of retinal neovascularization, with cell culture studies suggesting similar anti-angiogenic activity to sunitinib (Liang C, el al, A3272, 5-9th May 2013, ARVO, Seattle, WA).

We hypothesized that oral X-82 may have therapeutic potential as a treatment for neovascular age-related macular degeneration (AMD), given the known importance of VEGF in the pathogenesis and clinical course of neovascular AMD, and the potential

importance of PDGF in neovascular AMD.[6, 7] Neovascular AMD is the leading cause of vision loss in most developed nations.[8, 9] Treatment usually involves repeated intravitreous injections of anti-VEGF agents, but these impose a substantial burden on patients and healthcare providers. An oral treatment for neovascular AMD would have several obvious advantages. Most importantly, it might reduce or eliminate the need for intravitreous injections. It could treat bilateral disease and may reduce the likelihood of second eye involvement. We therefore aimed to undertake preliminary safety testing of oral X-82 to determine if larger, randomized controlled trials are justified.

METHODS

Study design:

This Phase 1, open-label, dose-escalation study (ClinicalTrials.gov Identifier: NCT01674569) received Institutional Review Board approval for all of the five US study sites, and was conducted in accordance with the tenets of the Declaration of Helsinki. All participants provided written informed consent.

Participants:

The study enrolled 35 male and female participants aged at least 50 years with active neovascular AMD, and ran from November 2012 to March 2015. Eligibility criteria are provided in the eAppendix 1. Participants could be anti-VEGF naïve, or have received prior anti-VEGF therapy.

Study visits:

Participants attended for screening, day 14, and then monthly for 7 months (210 days). The schedule of procedures is shown in eAppendix 2

Study treatment:

Groups of participants were assigned to one of seven X-82 doses over 24 weeks, with an additional 4 weeks for follow-up. The dose escalated from one level to the next in the absence of any DLT. Dose limiting toxicity was defined as a drug-related safety event during the first 2 weeks of treatment that was severe enough to require removal of the participant from the study. If a DLT ocurred in a given dose group, then the initial allocation of three participants was expanded to at least six. The Maximum Tolerated Dose was the maximum dose at which no DLT occurred in a group of three participants, or no more than one DLT in a group of six. The planned escalating dose regimens were 50 mg alternate days, 50 mg daily, 100 mg alternate days, 100 mg daily, 200 mg daily, and 300 mg daily.

Other permitted treatments:

Intravitreous anti-VEGF rescue therapy with 0.5 mg ranibizumab (Genentech, South San Francisco, CA), off-label 1.25 mg bevacizumab (Genentech), or 2 mg aflibercept (Regeneron, Tarrytown, NY) was permitted if predefined retreatment criteria were met (eAppendix 3).

Safety outcomes:

The safety outcomes comprised findings on ophthalmic examination, incidence of systemic and ocular AEs and serious adverse events (SAEs), DLT, discontinuation for drug-related AEs, and laboratory values. Adverse events were coded using the Medical Dictionary for Regulatory Activities' Preferred Terms, Version 17.1. Relatedness of the AE or SAE to X-82 treatment was determined by the reporting Principal Investigator.

Efficacy outcomes:

The predefined efficacy outcomes were change from baseline in mean BCVA, choroidal neovascularization (CNV) size, and CRT, proportion who develop CNV in the unaffected fellow eye, time to intravitreal anti-VEGF rescue therapy, and number of anti-VEGF injections.

Image analysis:

Fundus photographs and FA were acquired at baseline, month 3, and month 6 to monitor safety and CNV size. Monthly OCTs helped determine if anti-VEGF rescue therapy was needed. The automated measurement of central subfield thickness was prospectively collected by the investigator at each visit.

A post-hoc, central, masked assessment of the baseline and last available OCT for each participant was conducted using experienced, reading centre-certified graders. The following were determined as present or absent: subretinal fluid (and the extent of any fluid present), retinal cystoid changes, pigment epithelial detachment (and the extent, if present), subretinal fibrosis, and other retinal findings. The response to

treatment was thereby categorized as marked improvement, mild improvement, no change, mild worsening, or marked worsening.

Statistical Analysis:

No formal hypothesis testing was performed. Continuous variables are summarized by descriptive statistics. Discrete variables are summarized by frequencies and percentages. Two participants had bilateral disease (in both the right eye was the study eye). The safety population comprised all participants who received at least one dose of X-82. The efficacy population comprised all those who completed the course of X-82 treatment. Mean values are presented ±1 standard deviation, unless noted otherwise.

RESULTS

Patients demographics and disposition:

Of 35 participants, 28 had already commenced anti-VEGF therapy and seven were treatment naive. eTable 1 shows the baseline characteristics.

Figure 1 shows the disposition of participants and their dosing. Twenty-eight participants completed 3 months and 25 completed 6 months.

Safety outcomes:

Adverse events:

There were four ocular AEs in four of 35 participants (11.4%), comprising dry eye, meibomian gland dysfunction, retinal scar and vitreous floaters. Twenty-eight participants (80%) had at least one systemic AE (eTable 2). The majority were considered mild or moderate. Three AEs (8.6%) were considered severe: one case of multiple myeloma, one of pulmonary hypertension, and one with an isolated, five-fold increase in serum transaminase, which was reversible and not associated with other abnormalities (hence not considered an SAE). Of 94 systemic AEs, 32 were considered related to X-82 (Table 1).

Serious adverse events:

There no deaths and four SAEs in three participants (8.6%), none attributed to X-82. One 73-year-old participant was hospitalized with mild chest pain. Cardiac enzymes were negative and he was discharged on clopidogrel after angiography revealed no significant stenosis. A 95-year-old participant took 1 day of X-82, then elected to discontinue treatment. Two weeks later she developed acute renal failure and four days after that was admitted with congestive heart failure, from which she recovered. A 73-year-old participant discontinued X-82 due to leg cramps. Two week later she was diagnosed with multiple myeloma and commenced chemotherapy.

Dose limiting toxicity and discontinuation for drug-related adverse events:

Of 25 participants completing 24 weeks treatment, six discontinued X-82 due to AEs potentially related to X-82 (two in the 50 mg daily group, one each in the 100 mg daily and 200 mg groups, and two in the 300 mg group). Four discontinued due to unrelated events (eTable 3). Although no participants met our definition of DLT, two of three participants in the 300 mg group withdrew due to AEs attributed to X-82; one had mild anorexia, nausea and weight loss, the other had diarrhea.

Laboratory investigations:

Liver enzyme elevations were reported as AEs 10 times across five participants. Four participants exhibited raised transaminases. An 80-year-old female experienced AEs of fatigue, leg cramps, nausea, and faintness and withdrew from the study, having taken 50 mg X-82 daily for 10 weeks. Two weeks later her alanine transaminase (ALT) was 6 times the upper limit of normal (ULN) with aspartate transaminase (AST) 1.9 times the ULN. Both normalized over 6 weeks.

An asymptomatic 56-year-old male receiving 100 mg alternate days had ALT 3.3 times the ULN and AST 1.6 times the ULN at 3 month. By month 6, both had normalized despite continuing X-82.

An asymptomatic 71-year-old female receiving 100 mg daily had ALT 3.1 times the ULN and AST 2.7 times the ULN at month 3. X-82 was withheld and both normalized within 3

weeks. After rechallenging with 100 mg daily ALT rose to 1.6 times the ULN and AST to 1.5 times the ULN. X-82 was discontinued and transaminases normalized.

An asymptomatic 69-year-old female receiving 200 mg daily had ALT 8.4 times the ULN and AST 2.9 times the ULN at month 2. X-82 and atorvastatin were withheld. By month 3 ALT was 1.6 times the ULN and AST 1.1 times the ULN and she was rechallenged with 100 mg X-82 daily. The ALT rose to 3.6 times the ULN and the ALT to 1.6 times the ULN, within 1 week. X-82 was discontinued and both normalized.

An 82-year-old female receiving 300 mg daily had ALT 1.5 times the ULN at month 2. Values normalized when she discontinued X-82, due to diarrhea.

No other laboratory abnormalities were noted.

Efficacy outcomes:

Visual acuity:

In the 25 participants who completed 24 weeks of treatment the mean BCVA change from baseline was +3.8 ± 9.6 letters (Figure 2; eTable 4; eTable 5). The mean BCVA change across all 35 participants was +3.5 ± 9.7 letters. The 28 participants dosed at least daily gained +4.3 ± 9.2 letters.

Three participants (8.6%), dosed with 100 mg alternate days, 200 mg daily and 300 mg daily, had worsening of >5 letters.

Anti-VEGF rescue therapy:

The mean number of anti-VEGF injections in the 25 participants who completed 24 weeks treatment was 0.68 (median 0; range 0-4; interquartile range 0-1), with 15 (60%) not requiring any anti-VEGF rescue injections. The mean time to the first rescue injection was 130 days in the 10 participants who completed the study and required an injection. All doses except for 50 mg alternate days showed very low injection rates (Figure 3). The mean number of anti-VEGF injections in those who received at least 50 mg daily for 24 weeks was 0.4 (median 0; range 0-2; interquartile range 0-1). None of those assigned to 300 mg daily required intravitreous injections whilst receiving X-82. Previously treated participants who completed 24 weeks of X-82 treatment averaged 9.0 ± 4.1 injections yearly, prior to enrolment.

Central retinal thickness:

There was little change in OCT central subfield thickness at doses from 50 mg alternate days up to 100 mg daily, except for one participant in the 100 mg daily group who

showed a “marked improvement”. Five of seven participants receiving 200 mg had a reduction in thickness, as did two of three receiving 300 mg. None of these participants required anti-VEGF therapy. Reduced central subfield thickness was usually associated with improved vision (eFigure 1). The mean OCT central subfield thickness in those who completed 24 weeks of treatment reduced by -50 ± 97 μm (Figure 4). The greatest response occurred in treatment-naïve participants (eTable 5). No participants showed increased macular fluid whilst receiving X-82, 27 showed “no change”, two showed “mild improvement” and six showed “marked improvement”.

Angiography:

In the study eyes with baseline and final visit angiographic measurements (n = 27), there was minimal change in the Investigator-determined CNV area (+0.24 ± 3.1 disc areas). No participants developed new neovascular AMD in the fellow eye, but one (receiving 50 mg daily) developed new exudation from a previously treated fellow eye CNV.

Post hoc analyses:

There was no significant change in mean systolic (+0.5 ±15.3 mmHg, p 0.84) or diastolic (-2.6 ± 10.9 mmHg, p 0.19) blood pressure (n 35).

To investigate if anti-VEGF injections drove the VA and OCT improvements we analysed the 15 participants who received no anti-VEGF injections. The VA and OCT improvements were slightly better than than the entire efficacy population (central subfield thickness -53 ± 65 µm; BCVA +5.3 ± 9.1 letters).

DISCUSSION

Early phase studies such as ours are not sufficient to confirm the therapeutic benefit of X-82, but the results suggest it warrants further investigation. The main downside of treatment was elevated liver enzymes and gastrointestinal symptoms, that occurred in 11% and 14% or participants respectively. Of 35 participants, six (17%) did not tolerate X-82 and an additional four failed to complete the study. Thus, X-82 may not be suitable for all patients, but in those who tolerated X-82 there was the suggestion of reduced demand for anti-VEGF therapy, averaging only 0.68 injections over six months.

Of the 25 participants who completed the 24 weeks of X-82 treatment, 60% required no anti-VEGF injections, increasing to 72% if the lowest dose is excluded. Despite low retreatment rates, BCVA was maintained or improved in all participants. It seems unlikely that the vision gains are attributed mainly to anti-VEGF injections, given how few injections were given and because the greatest vision gains occurred in those not receiving injections. Further, a majority of participants in the 200 mg and 300 mg groups showed substantial OCT improvements in the absence of anti-VEGF therapy. Taken

374 together, these results suggest that X-82 has biological activity and reduces intravitreal
375 anti-VEGF therapy. A drug that reduces anti-VEGF therapy without sacrificing vision
376 would have considerable clinical utility.[10]
377
378 The most common AEs were fatigue, nausea and diarrhea, consistent with the early
379 phase study of X-82 for cancer and the known side-effects of sunitinib.[2, 3] The AEs were
380 generally mild or moderate and resolved with time or when X-82 was discontinued, as
381 did the mostly asymptomatic transaminase elevations, but larger studies are needed to
382 confirm these preliminary observations. The transaminase elevations did not appear to
383 be dose related and hence it is important to monitor liver function in all patients
384 receiving X-82, regardless of dose. If X-82 was adopted, then the transaminase
385 elevations and AEs may mean some patients need to discontinue X-82 therapy, but it
386 appears a majority of patients would tolerate treatment.
387
388 Considering both safety and efficacy, 200 mg daily may be the best dose. At this dose
389 there were no SAEs and a good VA and OCT response in the absence of anti-VEGF
390 injections. Given the relatively short half-life of X-82 (< 9 hours), twice daily 100 mg
391 dosing might also be appropriate.
392
393 A phase I dose escalation trial of another oral tyrosine kinase inhibitor, pazopanib, was
394 conducted in healthy volunteers, reported alongside a fixed-dose pilot study of 15
395 treatment-naïve participants with neovascular AMD (ClinicalTrials.gov Identifiers:
396 NCT01051700; NCT01154062). The authors reported that pazopanib was well

tolerated, with no withdrawals due to AEs.[11] Two of 72 (3%) healthy volunteers and none of those with AMD developed elevated transaminases, fewer than the current study (11%) but over a much shorter follow up (1 versus 6 months). Six (40%) participants with AMD required anti-VEGF rescue therapy before the day 29 endpoint. If we had reported our injection rate over the same interval, then only 6% of our participants required rescue injections. If we consider only our treatment-naïve participants (as with the pazopanib study), none required an injection in the first month. None of our participants had elevated liver enzymes in the first month.

Strengths of our study include its prospective design and longer follow up than other studies investigating oral tyrosine kinase inhibitors for neovascular AMD. The main weaknesses, inherent to most open-label phase I studies, are a small sample size and lack of both masking and a control group. Accordingly, the safety and efficacy results should be considered preliminary, and both require confirmatory studies prior to clinical adoption of X-82. For example, our study may be too small to detect rare thromboembolic events associated with anti-VEGF suppression. This study cannot determine the level of patient compliance with X-82 in a clinical setting. Wet AMD is often symptomatic and this might be expected to improve compliance, whereas any AEs might reduce compliance. Because 80% of our participants were already receiving anti-VEGF therapy at enrolment, this may reduce the potential for clinical improvement.

In summary, 29% of participants failed to complete the study and whilst not all withdrawals were due to AEs, many were, and hence the potential benefits of X-82

needs to be carefully weighed against the risks. However, in the 71% of participants who tolerated X-82 and completed the study, particularly those taking daily doses, there were far fewer than expected anti-VEGF injections. If it was established that X-82 offers an almost three-quarters chance of far fewer intravitreal injections, then it may yet be acceptable to many patients, however, larger studies are needed to confirm the balance of safety and efficacy. A Phase 2, randomized, double-masked, placebo-controlled trial of X-82 for neovascular AMD recently completed enrolment of 132 patients (NCT02348359).

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Conflict of Interest: C. Liang, D. O'Shaughnessy and E. Parsons were employees of Tyrogenex. J Slakter and P Rosenfeld are consultants to Tyrogenex. J. Slakter received research grant support for image evaluations for the trial. D. Boyer, D. Brown, N. Chaudhry, M. Elman and S. Patel were Principal Investigators and their practices received site payments for participants enrolled on this study.

Authors' contribution: All authors were responsible for the design of the study, interpretation of the data; and review and approval of the manuscript. TL Jackson prepared the first draft of the manuscript and revisions. C Liang, D O'Shaughnessy and E Parsons undertook data management and statisticial analysis. J Slakter led on image analysis. J Slakter and P Rosenfeld undertook image analysis.

Data access: C Liang, D O'Shaughnessy and E Parsons had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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FIGURE LEGENDS

Figure 1:

*Title***:** CONSORT flow diagram

Legend: Consolidated Standards of Reporting Trials (CONSORT) flow diagram, showing disposition of participants.

Figure 2:

Title: Visual acuity

Legend: The figure shows the mean change in Early Treatment of Diabetic Retinopathy Study visual acuity from baseline to week 24, in the 25 participants who completed 24 weeks of X-82 treatment. Error bars show the standard error of the mean.

Figure 3:

Title: Average number of intravitreal rescue injections versus X-82 dose

Legend: The graph shows the mean (± standard error of the mean) number of intravitreal anti-vascular endothelial growth factor rescue injections required, by dose group. The red columns show the 25 participants who completed 24 weeks of X-82 therapy, versus all 35 participants (shown in blue).

Figure 4:

Title: Central subfield thickness

Legend: Optical coherence tomography central subfield thickness for all participants who completed the 24 weeks of dosing. Thickness decreased somewhat overall as

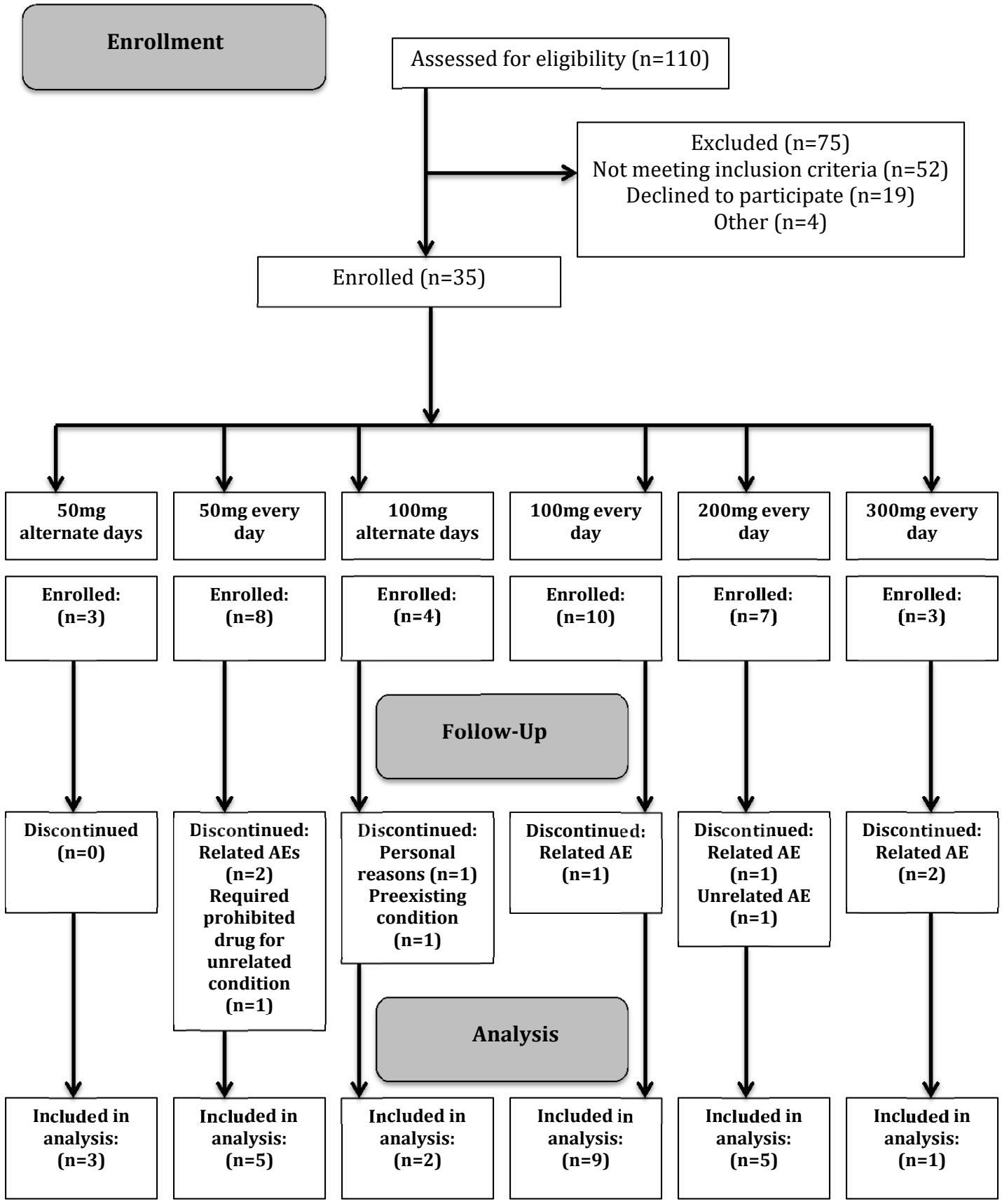
compared to baseline measurements, most notably in the naïve patients. Graph shows the mean ± the standard error of the mean.

Table 1: Adverse events considered related to X-82

System Organ Class[*]	**Event** (preferred term)[*]	**Grade of severity** (number of occurrences)				
		Mild	Moderate	Severe	Life-threatening	Fatal
Gastrointestinal	Abdominal discomfort	1				
	Abdominal pain upper	1				
	Diarrhea	1	3			
	Nausea	3				
General Disorders	Fatigue	4				
Investigations	Alanine aminotransferase increased	2	1			
	Aspartate aminotransferase increased	2	4			
	Liver function test abnormal			1		
	Weight decreased		1			
Metabolism and Nutrition Disorders	Decreased appetite		1			
Musculoskeletal & Connective Tissue	Muscle spasms		2			
Nervous System	Dysgeusia	2				
	Dizziness	1				
Renal & Urinary Disorders	Pollakiuria	1				
Vascular Disorders	Accelerated hypertension		1			

[*] As defined by the Medical Dictionary for Regulatory Activities (MedDRA, Version 17.10)

Figure 1: CONSORT Flow Diagram



AE = adverse event. Relatedness determined by site clinician. All participants included in safety analysis.

Figure 2: Visual Acuity

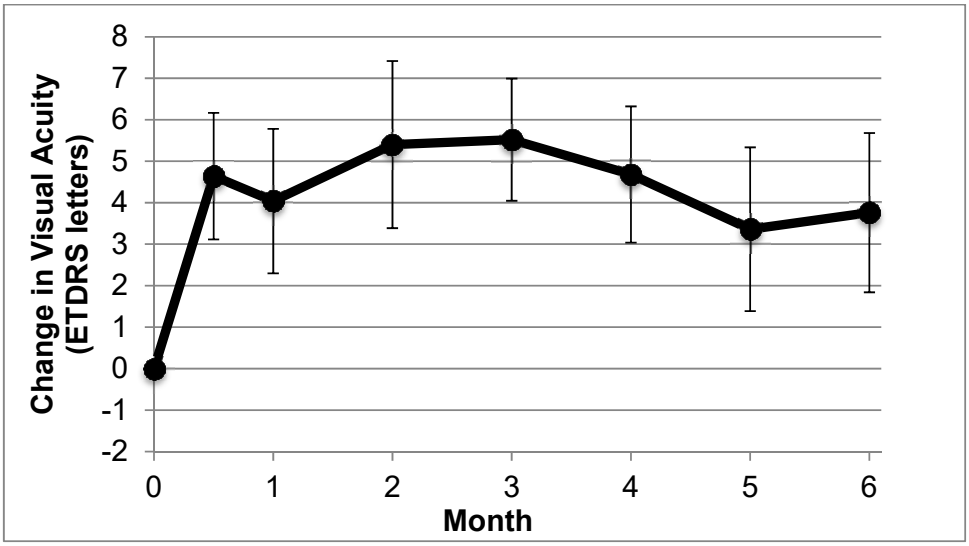


Figure 3: Average Number of Intravitreal Rescue Injections Versus X-82 Dose.

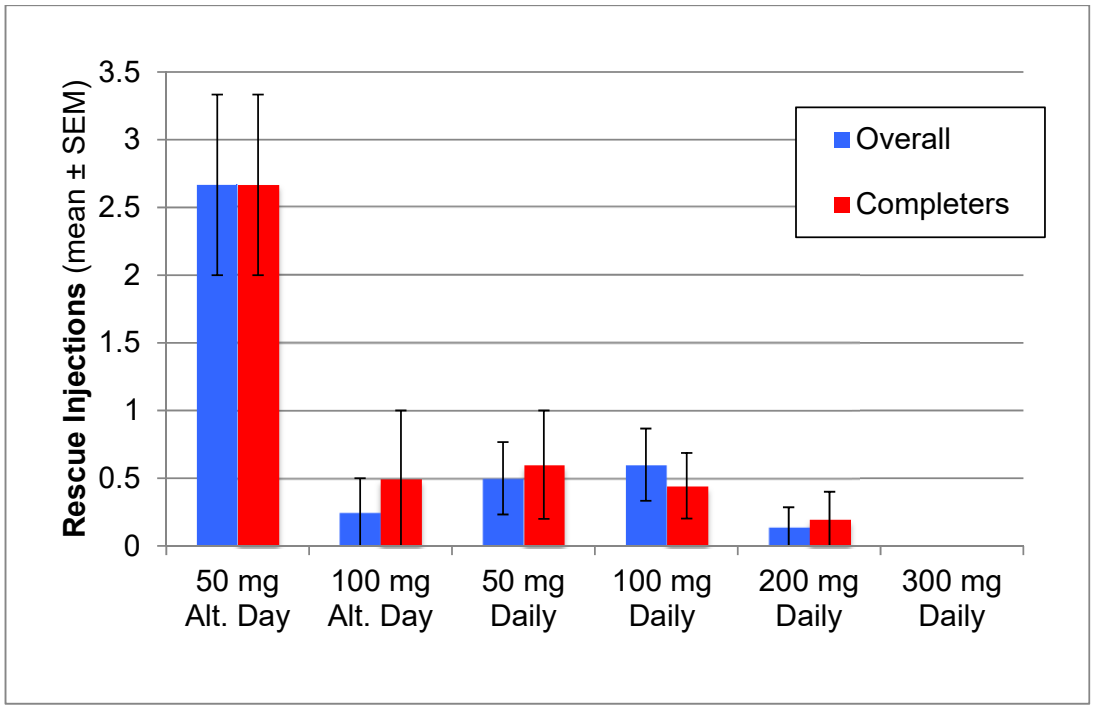


Figure 4: Central Subfield Thickness