APEX: A Phase II Clinical Trial Evaluating the Safety and Preliminary Efficacy of X-82 Administered Orally in the Treatment of Exudative Macular Degeneration

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BACKGROUND

- X-82 (vorolanib) is a multi-kinase VEGF/PDGF inhibitor that blocks kinase activity associated with all receptor subtypes for VEGF & PDGF
  - Earlier generations were limited by systemic toxicities
- Engineered to treat patients with pathologic angiogenesis found in certain solid tumors (VHL) and in exudative AMD

Results from Phase 1 Dose-Escalation Study in Exudative AMD:

- 35 patients (mostly sub-optimal responders, but 7 treatment naïve) all received varied dosages of X-82 over a six-month period
- 60% of patients required no anti-VEGF injections over that time
- No dose-limiting toxicities
- Most common adverse effects were GI and reversible elevations in LFTs (11%)

OBJECTIVE

- The safety and efficacy of X-82, an orally administered inhibitor of vascular endothelial growth factor and platelet derived growth factor, was investigated for treatment of wet AMD in a phase 2 clinical trial.
- **Primary outcome:** Change in ETDRS VA from Day -1 to Week 52 after randomization
- **Secondary outcomes:** number of anti-VEGF injections, retinal thickness, loss of >15 ETDRS letter, rate of conversion in fellow eye

METHODS

- Phase 2, randomized, double-masked, placebo-controlled trial enrolled subjects with a prior diagnosis of exudative AMD having received at least two intravitreal injections of anti-VEGF therapy.
- Subjects were randomized equally into four groups that received either daily 50 mg, 100 mg, or 200 mg dosages of X-82 or a placebo tablet.
- At each four-week interval visit for 52 weeks, subjects were to be assessed to determine if rescue treatment was needed with anti-VEGF therapy.
  - Treatment given if any increase in macular fluid or thickness compared or new, or increased, macular hemorrhage
- Lab work and urinalysis were performed at each monthly visit
- In addition to standard set of monitored safety parameters, several guidelines were set forth regarding careful monitoring of any elevation in liver enzymes
  - Regular meetings with specified Data Safety Committee

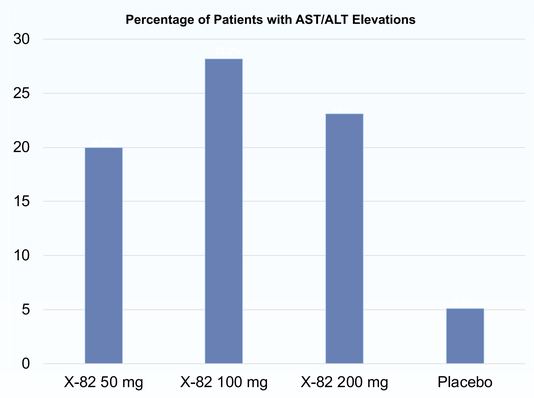
RESULTS

- Overall, 157 patients enrolled at 39 sites across the United States
  - The ITT average age was 75 years old.
- The study was stopped prematurely for insufficient benefit to risk ratio after the second planned interim analysis, which was conducted after 90% of patients had reached week 36
  - Concern for hepatobiliary toxicity
  - A total of 103 (103/157; 65.6%) subjects completed the study up to and including the Week 56 follow-up visit.

RESULTS

- The ITT population started with a mean visual acuity of 71.0 (n=157; Snellen 20/40) and ended with a mean of 72.3 (n= 81; Snellen 20/40) at week 52.
- The PP population started with a mean ETDRS BCVA score of 71.7 letters (n=92; Snellen 20/40) and ended with a mean of 71.2 letters (n= 68; Snellen 20/40) at week 52
- Statistically significant non-inferiority of visual acuity was demonstrated at the week 52 visit in all groups receiving X-82 when compared with placebo in both ITT and PP populations.
- Overall, 95.6% (87/91) of all patients lost fewer than 15 ETDRS letters by Week 52.
- Patients in the ITT population required an average of 6.4 intravitreal injections, with the 50 mg (n=40), 100 mg (n=39), 200 mg (n=39), and placebo (n=39) group requiring 6.7, 6.0, 4.7, and 8.1 injections respectively.
  - In the PP population (n=92) a similar trend was seen.
- There were several instances in which patients did not require another anti-VEGF injection after final screening treatment was completed.
  - This was dose-dependent, and more common in those receiving X-82 (7.5% (3/40), 10.3% (4/39), and 20.5% (8/39) in the 50 mg, 100 mg, and 200 mg groups, respectively) then those receiving placebo (2.6% (1/39)) but was not statistically analyzed and also does not take into account follow up time.
- Relative to only 5.1% (2/39) of patients in the placebo group who experienced elevated liver enzymes, 20.0% (8/40), 28.2% (11/39), and 23.1% (9/39) had elevated enzymes in the 50 mg, 100 mg, and 200 mg groups, respectively.
  - Most elevations occurred within 8-10 weeks of randomization.
  - Most commonly, liver enzymes returned to normal within a few weeks after discontinuation of X-82

Required Early Termination	
50 mg X-82	**5.0%** (2/40)
100 mg X-82	**15.4%** (6/39)
200 mg X-82	**17.9%** (7/39)
Placebo	**0.0%** (0/39)



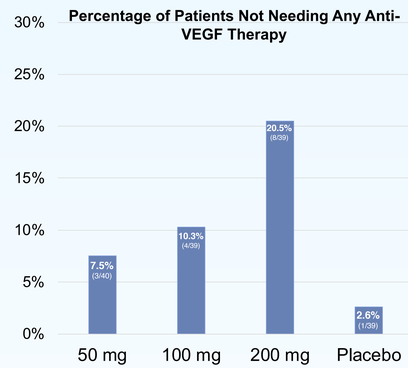
Visual Acuity Results – X-82 vs. Placebo

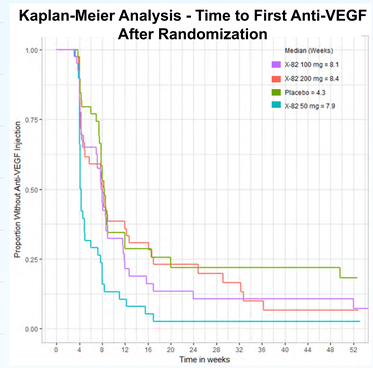
	50 mg X-82	100 mg X-82	200 mg X-82
Mean Change in VA from Baseline to Week 52	-4.02	-1.71	-2.33
P-value	<0.00001	<0.00001	<0.00001

CONCLUSIONS

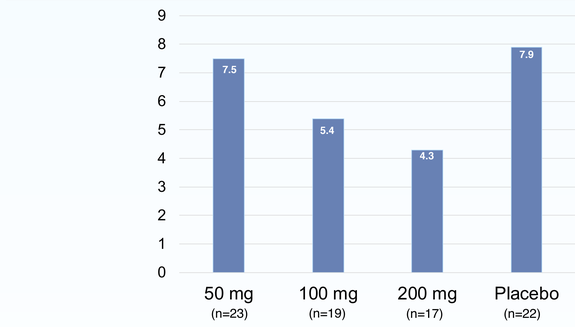
- X-82 oral therapy in combination with PRN anti-VEGF injections showed non-inferiority in visual acuity outcomes while achieving a dose-dependent decrease in the number of anti-VEGF injections compared with placebo.
  - Several patients did not require another anti-VEGF injection after initial screening treatment
- Given the limited tolerability and safety issues observed, X-82 does not have a sufficient benefit to risk profile in treatment of patients with AMD.

Less Demand for Anti-VEGF

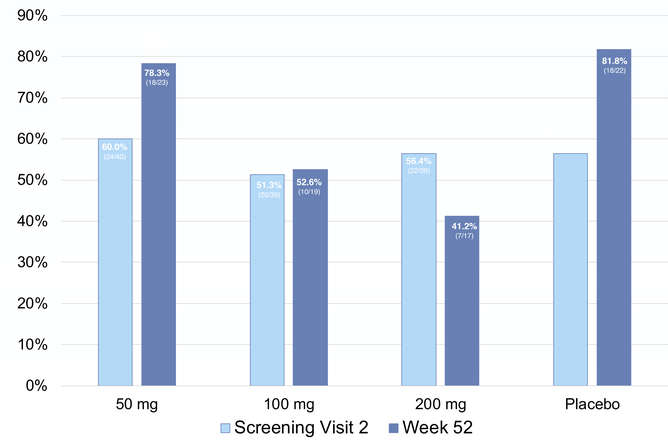




Mean Number of Anti-VEGF Injections in 52-Week Period



Percentage of Patients with Subretinal Fluid on OCT



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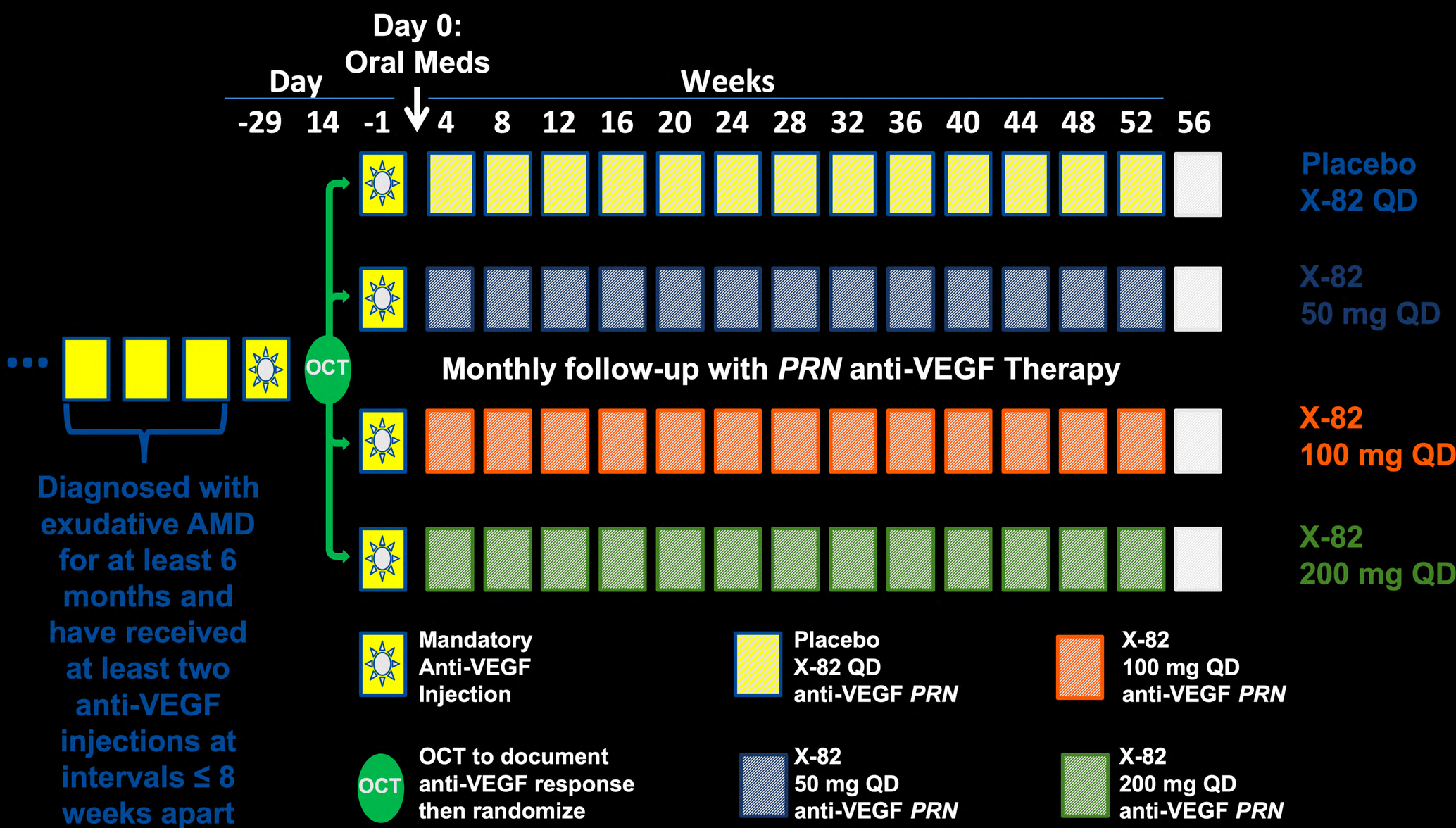
Study Design



Results

- 157 participants (39 sites)
- Stopped prematurely after the second interim analysis out of concern for elevated liver enzymes and gastrointestinal adverse events
  - Conducted after 90% of patients had reached Week 36
  - 103 (103/157; 65.6%) subjects completed study through Week 56

Baseline Characteristics		
Gender	Male	78/157 (49.7%)
	Female	79/157 (50.3%)
Age	Mean	75.0
	Standard Deviation	7.95
Race	Caucasian	154
	Asian	2
	Other	1
Visual Acuity	Mean	71.1 (20/40)
	Standard Deviation	11.83

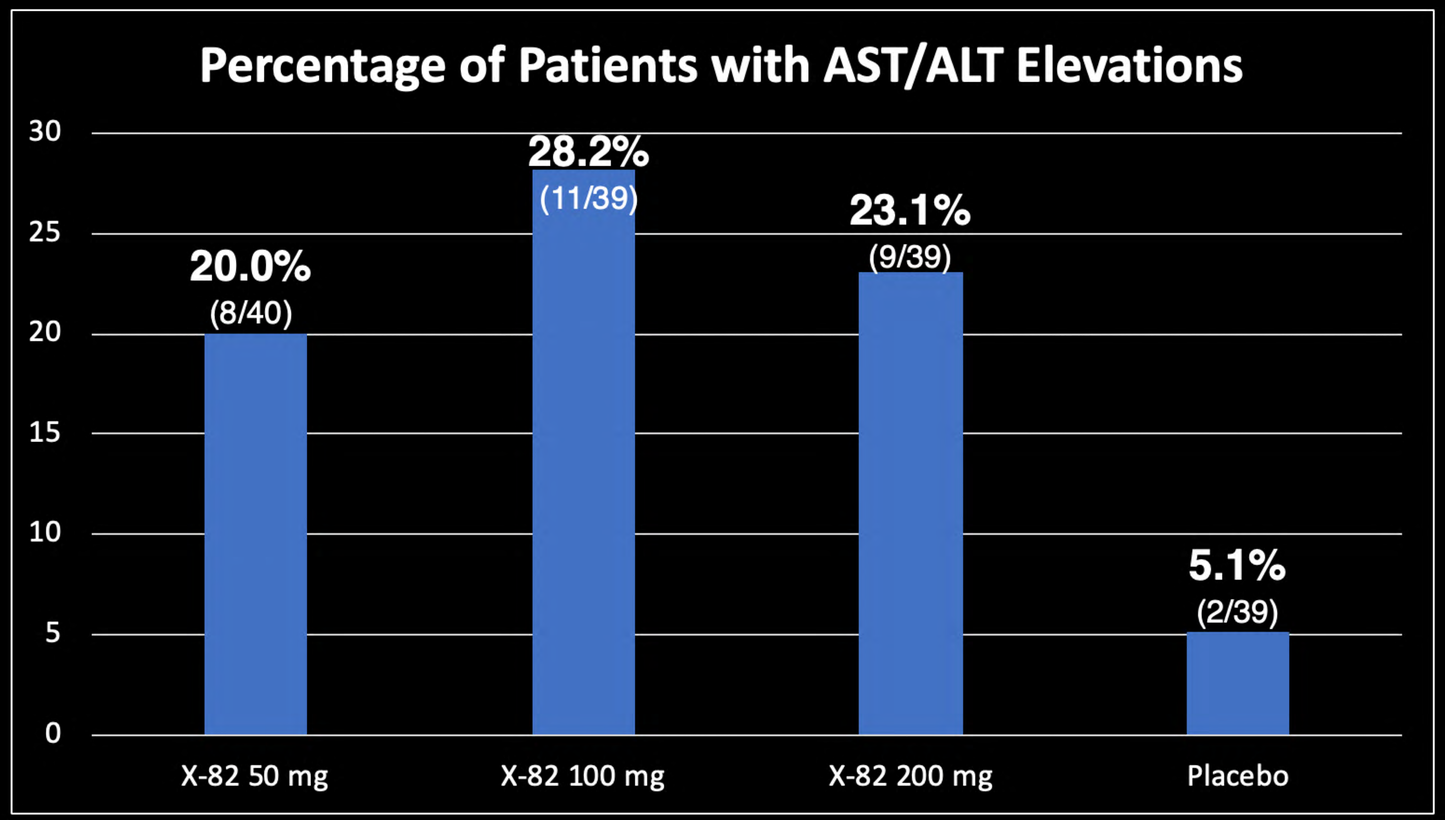
VA Results – X-82 vs. Placebo

	50 mg X-82	100 mg X-82	200 mg X-82
Mean Change in VA from Baseline to Week 52	-4.02	-1.71	-2.33
P-value	<0.00001	<0.00001	<0.00001

- Negative estimates indicate less loss (or better maintenance) of visual acuity compared to placebo

Adverse Effects

- Dose dependent response - diarrhea, vomiting, and fatigue
  - No patients in placebo group (n=39)
- Elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST)



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Placebo	0.0% (0/39)

Conclusions

- X-82 oral therapy in combination with PRN anti-VEGF injections:
  - Demonstrated non-inferiority in VA outcomes
  - Achieved a dose-dependent decrease in the number of anti-VEGF injections compared with placebo
  - Several patients did not require any anti-VEGF injections after initial screening treatment
  - Study was prematurely terminated due elevations in liver enzymes