Company: Atherogenics, Inc. (AGIX)
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We began reviewing AtheroGenics, Inc. (AGIX), as a short thesis, soon after this past January's "H&Q" Conference. Our interest was based on the Company's 1) growing market capitalization predicated on 2) undue optimism in anticipation, late this summer, of clinical trial results from the company's first drug. This optimism has been supported over the past 6 months by secular events including 1) heightened interest in cardiovascular (CV) disease (statin drugs, stent devices) and 2) Pfizer's end-of-year acquisition of Esperion Therapeutics for $1.3 billion. Esperion was at an earlier stage of clinical development than AtheroGenics.

AtheroGenics closed on March 26 at $20.82, giving it a market capitalization of $770 million based on 37.0 million shares outstanding (35.0 million float). The average daily volume (90 day) is ≈ 528,000 shares, but shrinking (379,000 in last 10 days). Unfortunately, the short position has expanded in each of the past three months and in March was at 4.28 million shares (9.5 days and 12 percent of the float), up from 4.12 million (5.5 days and 12 percent) in February and 3.89 million in January. In August 2003, the Company issued $100 million of 5-year, 4.5% securities which convert at $15.34.

At fiscal year end December 31, AtheroGenics reported $132 million of cash and equivalents ($3.57/share) and no revenues in 2003 or 2002. AtheroGenics had an accumulated deficit of $143 million since its founding just over ten years ago.

Conclusion: There will be three inflection points for AtheroGenics. The first is the possible announcement of a corporate partner, which could be a positive for the stock. The Company is behind plan on this goal, since a partner was expected by year end. Since the former Vice president of Business Development "resigned" after a year-and-a-half and his replacement just joined this month, a deal before August seems unlikely. Still, if a deal is announced before early summer, it will likely be viewed as validation, an endorsement. However, to the extent that the deal is back-end loaded, it could signal skepticism of clinical success. Second, in late August the Company will report (possibly at the European Society of Cardiology Conference, August 28, 2004) Phase 2 data from the CART-2 clinical trial of lead drug '1067. Like the first Phase 2 trial (different dosage, duration of treatment, new endpoint), the PCE is a surrogate marker of CV disease, intravascular ultrasound (IVUS)-based coronary artery patency, post-PTCA. The third event (and most likely to disappoint) will be the announced results from the Company's Phase 3 trial (ARISE) of '1067, which began June 30, 2003, and, as a DB-PC, will enroll 4,000 patients (post-AMI, not PTCA) for treatment over an 18mCOT. The PCE is 20 percent decreased MACE (AMI, stroke, unstable angina) versus SOC or 1,160 events. The leap of faith from a surrogate endpoint (retrospective analysis in the first Phase 2, prospective analysis in the second trial) to clinical endpoints (Phase 3) puts this pivotal trial at a very high risk of failure. These data are not expected until Q3/05.

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Introduction:

Founded in November 1993 by Emory University cardiologists Russell Medford, MD/PhD (Pres/CEO) and Wayne Alexander, MD/PhD (Director and Chairman Department of Medicine at Emory), the Company raised almost $40 million from venture investors over the next six years. Two events, the signing of Schering-Plough as a corporate partner in October 1999 ($189 million biobuck, $5.0 million up-front) and the end-of-millennium market bubble enabled AtheroGenics to complete a distressed public offering. The Company intended to raise $72 million at $203 million pre-money (6.0 million shares at $11.00 to $13.00), but was only able to raise $55 million (with the shoe) at $135 million pre-money (6.9 million at $8.00).

In September 1999, AtheroGenics initiated a Phase 2 clinical trial of its lead drug, '1067, a probucol analog, to prevent restenosis in patients receiving percutaneous transluminal coronary angioplasty (PTCA or angioplasty). The trial enrolled ≈ 300 patients into five arms, three drug dosages, placebo and probucol (positive control). The trial was conducted in Canada, where probucol is approved, since FDA had withdrawn the drug from the US market in December 1995 due to serious CV side effects. Patients were treated for six weeks.

In May 2001, results from this trial (called CART-1) indicated marginal success, versus placebo, for '1067 at the highest dosage, but worse performance than probucol. A retrospective analysis of the intravascular ultrasound (IVUS) data, which was used along with conventional quantitative angiography to measure restenosis rates, found reduced atherosclerosis in the untreated coronary artery, although a dose response was not observed.

Therefore, in December, 2001, the company initiated a Phase 2 trial (CART-2) to prospectively test the conclusion drawn from CART-1. These data are expected to be reported in August 2004. There is no DSMB review or interim analyses planned. The last of 500 patients was enrolled on August 6, 2003. The double-blind trial will randomize PTCA patients to 280mg of '1067 (the highest dose tested in CART-1) versus placebo for a twelve month treatment period (versus six weeks in CART-1). The PCE is IVUS-based patency.

Finally, under a Special Protocol Assessment obtained from the FDA in March 2003, AtheroGenics initiated (June 30, 2003) a 4,000 patient Phase 3 trial ("ARISE") of '1067 in a different patient population, treated 50 percent longer and with a different PCE from those criteria employed in CART-2.

This report focuses on '1067's clinical development, since that will be the key driver of AtheroGenics's stock over the next 18 to 24 months.

Probucol and '1067

In 1971, the FDA cleared Marion Merrell Dow's Biphenabid (probucol, itself an analog of BHT, a common antioxidant added to food) to lower cholesterol. Rather than blocking cholesterol synthesis, like the statins (the first, Merck's Mevacor was approved in August 1987), probucol was believed to accelerate LDL ("bad" cholesterol) breakdown and slightly block dietary cholesterol absorption. In fact, the drug has a more robust effect on lowering HDL ("good" cholesterol) than on lowering LDL while having little or no effect on serum triglycerides. At best, probucol was a weak drug and, since almost 90 percent of the drug was not absorbed from the gut, its high dosage and limited effect on serum cholesterol were not surprising. Unfortunately, probucol was clearly linked to serious adverse cardiovascular side effects including QTc prolongation, Torsades de pointes and sudden death. Given an inferior risk-benefit scenario and the availability of superior drugs, FDA withdrew its marketing approval in December 1995 for what had since been renamed (Hoechst's) Lorelco.

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Probucol is a bilaterally symmetrical molecule, exhibiting what is also called mirror symmetry. In nature, for example, the left half of the butterfly and its mirror image depict the whole butterfly. Trying to retain the beneficial activity of probucol while reducing its CV side effects, AtheroGenics chemically modified one side of the molecule (as the succinate ester). Since they are chemically identical, it is actually much easier to modify both halves. Presumably (and recently confirmed by personal communication with AtheroGenics' senior chemist), the Company observed that the monosubstituted molecule ('1067) retained the desired activity while the disubstituted molecule was inactive. This explains the relatively low yield of '1067 at only 28 percent, as published by AtheroGenics in July 2002. Given the higher molecular weight of '1067 and the fact that only half of the molecule is active, dosing '1067 at 280 milligrams, once per day represents about 12 percent of the activity (on a molar basis) from dosing probucol at 500 milligrams, twice a day. As noted below, an almost ten-fold lower effective dose may account for the absence of CV side effects. However, this may also diminish '1067's desirable activities as well.

Clinical Development
CART-1

Initiated in September 1999 as a Phase 2 trial of '1067 efficacy in *restenosis*, CART-1 (Canadian Antioxidant Restenosis Trial) enrolled over 300 patients into five arms. This DB-PC study tested three dosages of '1067 versus placebo or probucol (positive control). The trial's PCE was restenosis measured by IVUS at ≈ six months post PTCA. Oral medication was administered for two weeks before and four weeks after intervention and all patients received daily aspirin while stented patients (85 percent) also received the anti-platelet drug clopidogrel (Plavix) for 30 days after PTCA. In addition to IVUS of the treated vessel, IVUS of an untreated vessel, QTc prolongation and serum lipids were also measured.

Summary of CART-1 Results

	PCE Restenosis at *target* vessel (2-D IVUS; mm^2)	Volume Change from baseline in a *control* vessel (3-D IVUS; mm^3)	Percent w/ QTc Prolongation of > 60msec	HDL ("good" cholesterol) *@ 6wCOT*	Restenosis *rates* at target vessel
Placebo (N=61)	2.66±1.58	-5.3±18.3 (N=42)	4.8% (N=53)	↓ 0.2%	37.5% *worst*
'1067 (N=59) (70mg, q.d.)	2.75±1.76 N.S.	-2.4±17.7 (N=41)	4.8% (N=48)	↓ 4.4%	---
'1067 (N=64) (140mg, q.d.)	3.17±2.26 N.S.	+3.5±21.4 (N=38; p=0.05) *best*	2.4% (N=50) *p=0.02 for '1067 as a group)*	↓ 9.0% (p<0.01)	26% as a group (p=0.09)
'1067 (N=61) (280mg, q.d.)	3.36±2.12 (p=0.046)	+1.8±21.3 (N=42)	2.5% (N=46)	↓ 18.7% (p<0.01)	---
Probucol (N=60) (500mg, b.i.d.)	3.69±2.69 (p=0.01) *best*	-0.2±16.9 (N=48)	17.4% (N=53)	↓ 35.1% (p<0.01) *worst*	25.5% N.S.

Patients were censored if they did not take at least 80 percent of their medication. Also some angioplasties were not successful, so the number of patients for each analysis above (only PCE is ITT) was typically less than enrolled. There was no statistically significant change in LDL levels in any cohort. It is clear that on an intent-to-treat basis, probucol was the best drug in terms of solidly hitting the PCE. The Company's exploratory analysis (second column, above) suggests a dramatic effect of '1067 on control vessel volume, however there is no dose-response effect and the best dosage (140mg) barely hits statistical significance. In fact, this particular result is from only 38 of 64 patients dosed at 140mg. Further, there is significant variability in volumetric measurements (note +3.5±21.4 mm^3 for the 140mg group) in each of the patient cohorts. This is like listening for a whisper in a crowded bar. These small absolute differences are of highly questionable clinical relevance.

Unfortunately, '1067's side effect profile, while improved when compared with probucol, remains problematic. The prolongation of QTc is significant, versus placebo, for the 144 patients receiving '1067 as a group. More worrisome is the dramatic, dose-dependent decrease in HDL observed with '1067 after only six weeks of treatment. There is consistent, correlative data supporting HDL's protective effect in CV disease; however, a direct link between increased HDL and decreased MACE (major adverse clinical events, typically, death, AMI or stroke) has not been demonstrated. Still, '1067's effect, like probucol, on lowering HDL may prove to be its greatest risk in the 12 month CART-2 and ARISE studies.

The initial results of CART-1 were released in May 2001. In October, Schering-Plough relinquished all rights to '1067 back to the Company, after two years and $8.0 million invested (of $189 million originally contemplated).

CART-2

AtheroGenics' conclusion that '1067 reverses atherosclerosis prompted a second Phase 2 study to prospectively test this hypothesis. As in CART-1, the trial again planned to target restenosis (IVUS-based) as its PCE (see below) and would also test the need for a two-week pre-PTCA dosing regimen. In December 2001, the Company began enrolling 500 patients scheduled to receive PTCA. The DB-PC study was to be conducted at 24 Canadian sites with patients receiving '1067 dosed at 280mg q.d. for a 12mCOT. No DSMB or interim analysis was planned. A related study (*DART*) wwas designed to test only Type 2 diabetics (and for only six months) in a similarly constructed clinical trial.

In June 2002, the Company met with FDA to discuss initiating, under an SPA, a Phase 3 trial of '1067. After that meeting, AtheroGenics decided to forgo restenosis as the PCE in the CART-2 study. Thus, in August 2004, the Company will report, as the PCE, '1067's effect on atherosclerosis based on the change, from baseline, in plaque volume in untreated coronary arteries.

The last patient was enrolled in CART-2 in July 2003 (announced in August). Results could be announced at or prior to the European Society of Cardiology conference (starts August 28) being held in Munich, Germany this year.

A positive result will lend investor support to AtheroGenics, despite the lack of objective evidence that a surrogate marker (an anatomical measurement) such as IVUS-based plaque reduction is predictive of improved clinical outcomes. Should the trial fail to demonstrate a compelling result, a stock price decline of 30 percent would not be surprising. In addition, this would force the Company to acknowledge that the ARISE trial (see below) is so different from CART-2, that predicting clinical outcomes based on surrogate markers is imperfect at best.

ARISE

By February 2003, AtheroGenics was on track to begin a pivotal Phase 3 trial of '1067 under FDA's SPA program. The SPA (Special Protocol Assessment) is FDA's written confirmation of, and agreement to, a pivotal trial design, PCE, eligibility criteria and treatment sufficient to support an NDA filing. In the absence of unforeseen adverse events, FDA is committed to approve the drug if all criteria are met. Unlike a typical IND plan, an SPA proposal from the sponsor includes a detailed statistical analysis plan. From the Company's perspective, the loss of statistical "flexibility" (e.g., retrospective analyses) is balanced by the implied certainty of a positive FDA review of the trial's results.

On June 30, the Company enrolled its first patient in the ARISE (Aggressive Reduction of Inflammation Stops Events) trial. This is a DB-PC study in 4,000 CAD patients who will receive SOC medications (cholesterol, hypertension, anti-platelet) ± '1067 (300mg q.d.) at 180 sites in N.Am, the UK and S. Africa. The study is event driven (1,160 events) and 95 percent powered to detect a 20 percent reduction in MACE (CV death, AMI, stroke, unstable angina requiring hospitalization, PTCA or CABG) after an 18mCOT or, at minimum, when the last patient completes a 12mCOT. Patients can enroll in the trial if they have had unstable angina (requiring hospitalization) or an AMI within the past year. Patients are excluded if they have had PTCA within the past 30 days. Enrollment is expected to be completed by June 2004. No DSMB reviews are planned.

Risk Assessment

- *Experimental Phase 3 Trial* AtheroGenics' Phase 3 trial (ARISE) reflects a giant leap of faith based on modest results from a retrospective analysis in a small patient population. In addition, the patient populations (PTCA versus AMI) are very different between the CART and ARISE trials, as are the endpoints (IVUS-based patency versus MACE) on which success is predicated. Finally, the SOC control arm in each trial is significantly different. Specifically, the ARISE patients will receive best medical treatment including drugs to reduce cholesterol (e.g., Lipitor), hypertension (e.g., ACE-inhibitors) and thrombus formation (e.g., Plavix). It seems highly unlikely that '1067's modest atherosclerosis blocking activity (combined with its significant and possibly deleterious reduction of HDL) will result in a 20 percent decline in clinical events.

  It is also surprising that ARISE expands the COT from six weeks to 12 months (at the highest dosage) with no planned interim safety reviews. Presumably, a sufficient cohort of CART-2 patients had been treated long enough (CART-2's 18 month enrollment was completed about two months after ARISE enrolled its first patient) to provide a supportive safety database. During the 6wCOT in CART-1, there were no statistically significant differences in clinical outcomes. For example, there were no deaths and 11 AMIs (2 with placebo, 3 with probucol and 1, 3 and 2 with escalating '1067). Finally, the revascularization rates ± stent were: placebo (18.3%/17.4%), probucol (18.0%/15.6%), '1067 at 70mg (16.9%/10.6%), 140mg (14.1%/13.7%) and 280mg (13.1%/6.2%; p=0.09 versus placebo with stents). Results for other clinical events (unstable angina, stroke) were not reported and were presumably zero. The short duration of treatment and small number of patients in each arm prevent any extrapolation of clinical outcomes in ARISE.

- *Questionable Drug Superiority* Probucol is marketed outside the US, for example in Canada, to reduce restenosis. However, the dramatic improvement in restenosis rates using drug-eluting stents in the US has nearly obviated any need for systemic therapy. Probucol's adverse side effect profile further justifies its removal from the US. AtheroGenics' chemical modification of probucol appears to "hit" one of the molecule's two active sites, in one sense making the drug half as active. Further, by lowering the dosage more than three-fold (from 1,000mg to 300mg, per day), the Company should have mitigated at least some of probucol's effects (compare QTc and HDL effects). However, it is not clear that AtheroGenics has identified '1067's therapeutic index and as such, the drug's reduced adverse effect profile may turn out to parallel a reduction in its putative therapeutic benefit, if one exists at all.