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Company: Corgentech, Inc. (CGTK)
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We began reviewing Corgentech, as a long thesis, after your positive one-on-one meeting with Management at [text redacted by author...]. Our interest was based on the Company's 1) reasonable market capitalization and strong balance sheet resulting from its February IPO, 2) scientifically rational, easily assimilated ex-vivo treatment, without competition, for a well-recognized unmet medical need and 3) late-stage clinical status with two large Phase 3 trials fully enrolled.

Corgentech closed on June 23 at $14.51, giving it a market capitalization of $402 million based on 27.7 million shares outstanding (6.9 million float). On August 12, the 180-day lockup expires on 20.8 million shares. Beneficial for the overall float longer term, the near-term may see some selling pressure. The average daily volume (90 day) is somewhat low and shrinking at ≈ 86,000 shares. Finally, the short position expanded from 129,000 in April to 432,000 shares (5.6 days) in May.

Corgentech's successful IPO priced on February 12 at $16.00 per share, the top end of its range, and for 6.9 million shares (includes green shoe), above the 5.0 million contemplated. Lead bankers were CSFB and Lehman with CIBC and Piper Jaffray also participating. For the fiscal first quarter ending March 31, Corgentech reported $152 million of cash and equivalents ($5.49/share) and no product revenues since inception. Corgentech had an accumulated deficit of $109 million and reported paid-in-capital of $261 million since its founding in January 1999.

Corgentech's lead molecule, CGT003 ('003) is an E2F inhibitor in Phase 3 testing to treat vein graft failures in both peripheral and coronary artery bypass grafts. Last October the Company licensed to Bristol-Myers Squibb its worldwide rights to '003 in all indications for $250 million. The deal's structure included $25 million in up-front licensing fees, $20 million in equity (2.08 million shares at $174 million pre-$) and up to $205 million in regulatory milestones. If '003 is commercialized, the Company will split US profits 50/50 and receive an estimated 15 percent royalty on OUS sales. There is the additional potential for $320 million in sales milestones.

Conclusion: A long position in Corgentech carries unacceptable risk. The Company's lead drug, edifoligide, may have utility in preventing vein-graft failure, but that utility has yet to be demonstrated. Corgentech has completed enrolling patients into two different Phase 3 trials under a single IND and success in both is required for an NDA submission, planned for Q2/05. A near-term interim analysis of the placebo event rate in one trial can have only two outcomes, no news or bad news. The 180-day lockup from Corgentech's February IPO expires August 12. Ownership of Corgentech's lead drug is split with Bristol-Myers Squibb and this deal was completed after both Phase 3 trials were fully enrolled. With a market capitalization of roughly $400 million and $150 million of cash, Corgentech may also be too small and too thinly traded to support an active short thesis.

Introduction:

Based in South San Francisco and venture backed (Trinity Capital, Interwest, Alta Partners, J.P. Morgan, HBM BioVentures), Corgentech combines a simple, ex-vivo pressure device to deliver an oligonucleotide into cells in order to block their proliferation (hyperplasia). Victor Dzau, MD at Brigham and Women's hospital in Boston developed the oligonucleotide and Michael Mann, MD, originally at B&W and currently at Stanford University developed the pressure-mediated transfection device. Both are scientific Founders of the Company. The company is targeting two indications for '003, peripheral bypass graft (PBG) and coronary artery bypass graft (CABG) and has completed enrollment in two Phase 3 clinical trials. [Text redacted by author]

E2F and Vein Grafts

For vein grafts used in coronary bypass or peripheral artery bypass, smooth muscle cell proliferation is a common cause of vein graft failure. The Company's molecule, also called *edifoligide*, is a 14 base pair oligonucleotide that closely matches the DNA sequence bound by a protein called *E2F*, a so-called transcription factor. Transcription factors (of $\approx$ 2,000 transcription factor in humans, six E2F variations have been identified) are found in the cell's nucleus where they bind to the DNA. This binding controls (up- or down regulates) specific DNA transcription to messenger RNA, which after leaving the nucleus is translated to protein. E2F activates genes related to cell proliferation. Thus, edifoligide acts as a decoy, soaking up E2F and thereby preventing gene activation and ultimately, cellular proliferation.

Veins obtained from the inner thigh (the saphenous veins are large, straight and somewhat redundant) are commonly used (grafted) to bypass blocked arteries that feed the heart or the lower limb extremities (e.g., a problem common to diabetics). However, once comparatively thin-walled veins are placed in the high-pressure arterial circuit, certain smooth muscle cells proliferate and migrate to the inner surface of the vein. These cells cause a buildup of lumenal plaque, reducing blood flow. The process is called neointimal hyperplasia and edifoligide halts this process.

Fortuitously, it appears that blocking cell proliferation results in the venous wall's thickening by a different mechanism, cell enlargement (hypertrophy). The enlarged smooth muscle cells strengthen the venous wall (comparable to an arterial wall) enabling it to tolerate the increased pressure of the arterial system.

This report focuses on the clinical data supporting Corgentech's Phase 3 trials, their design and likelihood of success. Data from both Phase 3 trials are expected in Q4/04 (PBG) and Q1/05 (CABG) with a single NDA filing expected in Q2/05. A third indication for edifoligide is in Phase 2 and a different decoy is being developed to treat eczema. These are less relevant to Corgentech's valuation for at least another year.

Clinical Development

From my discussion with [text redacted by author]...it became clear that '003's chemical design was given minimal consideration beyond its sequence identity to E2F's DNA binding site. Specifically, '003 is a 14-mer oligonucleotide of which only 10 nucleotides on each strand Watson-Crick base pair into the active duplex (double strand). The extra four nucleotides (inexplicably 5'$\rightarrow$3' on one strand, 3'$\rightarrow$5' on the other) on either end of each strand are superfluous; apparently, they are a structural remnant from other intentions for the molecule. [Text redacted by author] did not know what purpose they may have served when '003 was developed in Dr. Dzau's laboratory. The structure was made public (by Degussa Fine Chemicals, at least) in 2003.

It appears that the same lack of refinement applied to '003 continues in Corgentech's clinical development program. Specifically, both Phase 3 trials were each predicated on a single Phase 1/2 clinical trial, each conducted at one investigative site. While the ex-vivo use of '003 avoids considerations of ADME, rigorous dose-ranging studies to identify the therapeutic index and the likelihood of drug-related toxicities, there remains a genuine risk of systematic error in both Phase 2 studies. Further, the PCE for each of the Phase 3 trials had not been tested in either of the predicate Phase 2 studies, making both Phase 3 trials fundamentally experimental. It is worth emphasizing that '003 does not appear to be at all toxic or damaging to the treated venous tissue.

Finally, the PBG and CABG Phase 3 trials are being conducted under the same IND. A conventional NDA submission requires data from two successful Phase 3 trials. Thus, in theory, the failure of either trial to reach its PCE with statistical significance could be sufficient cause for FDA to reject an NDA submission. It is not clear what options Corgentech might pursue under this single failure scenario.

PBG

A summary of relevant PBG-related events, in raw format, from my database is provided below.

1/97:	Dzau et al. Ph 1/2 begins ("Prevent 1") for *'003* in PBG; DB-PC; inguinal bypass grafts; 1st 5 pt.s open label (safety), then 41 Pt.s (21 ♂) DB at 1 site (Brigham & Womens);
1/99:	Ph 1/2 data for *'003* in PBG;
10/30/99:	Lancet, 354; Mann et al. "Prevent 1" of 41 pt.s (3 cohorts) as no treatment (N=16), scrambled oligo (N=8), *'003* (N=17; 40µM); Endpoints were ↓ gene expression; BrdU incorporation ↓ 73%; Also ↓ graft occlusion, revisions, critical stenoses at 12mFU;
8/17/01:	IND cleared for Ph 3 in PBG;
11/12/01:	WSJ AHA; Ph 3 begins ("Prevent 3") of *'003* (40µM) in PBG (150k in US/year); DB-PC in 1,400 Pt.s at 80-84 N.Am. sites; PCE (needs 29% risk reduction, from 29% to 21%) is *time-to-failure* (w/in 12 months) as repair procedure or limb amputation, assessed at 1-, 3-, 6-, 12mFU; Technical failures excluded from ITT;
10/1/03:	Ph 3 enrollment done (2nd, "Prevent 3") for *'003* in PBG; N=1,400; *but*, technical failures (no blood flow via U/S at surgery) are censored;
4/27/04:	CIBC Conf.; Prevent 3 (PBG) needs 28% ↓ in failure; Drug (21%) vs placebo (29%); DSMB met; High surgical failure rate (oye);
11/04E:	AHA? Ph 3 data for *PBG*; Last Pt. FU done 11/30/04;
Q2/05E:	Submit NDA;

There are several important points worth highlighting. In the Phase 2 study, only 17 patients were actually tested with drug. And, as noted previously, all patients were tested at the same facility by the same physician. Also, only surrogate endpoints were used to assess efficacy. No clinical outcomes, as required for the PCE of the Phase 3 study, were reported. While the experimental design is commendable, especially the inclusion of a "scrambled oligonucleotide" arm, Corgentech has taken a significant leap of faith in order to enter a pivotal Phase 3 study with bona fide clinical endpoints. Variability between investigative sites/physicians and substantial uncertainty about the true event rate in the placebo arm place this study at a genuine risk of failure. Finally, there is a potential for subjectivity in the nominally objective quantitation of so-called technical failures. These failures, and their pre-specified exclusion from the ITT population, may confound or otherwise compromise interpreting the data set's relevance to real-world PBGs. Based on the data made available by Corgentech, this Phase 3 trial appears at very high risk of clinical failure due to a lack of statistical significance between the treatment and the placebo arms.

The PBG trial completed enrollment last October, on schedule. Data are expected late this year, though probably not at the AHA. A recent discussion with [text redacted by author] only confirmed that the PBG trial would be completed this calendar year and that complete data from both Phase 3 trials would be made fully available in Q1/05.

CABG

A summary of relevant CABG-related events, in raw format, from my database is provided below.

3/99:	Ph 2b begins ("Prevent 2") for *'003* (40µM) in CABG; DB-PC in 200 Pt.s at *1 site* (Siegburg, Germany); PCE is *composite of* % of Pt.s w/ ≥ 75% blockage (angiography) and death at ≥ 12mFU; Triple blind w/ angiography quantitated by Stanford Core lab; ITT includes Pt.s w/ angiography prior to 12mFU (due to AE); PRoject of Ex-Vivo Vein graft ENgineering via Transfection;
2001:	S-1; Ph 2b done for *'003* (40µM) in CABG; DB-PC in 200 Pt.s (99 placebo); ITT hit PCE as E2F (*27.7%*) vs placebo (*40.0%*), p=0.02;
3/20/01:	*Fast track* for *'003* in CABG;

11/12/01: WSJ AHA; Ph 3 begins ("Prevent 3") of *'003* (40µM) in peripheral artery BG (150k in US/year); DB-PC in 1,400 Pt.s at 80-84 N.Am. sites; PCE (needs 29% risk reduction, from 29% to 21%) is *time-to-failure* (w/in 12 months) as repair procedure or limb amputation, assessed at 1-, 3-, 6-, 12mFU; Technical failures excluded from ITT; Ph 2b data ("Prevent 2") Eberhard Grube et al. (late-breaker), for *'003* in CABG; DB-PC (1 site) of 200 enrolled, 136 evaluable w/ 309 SVGs; '003 (N=75, 47/172 vessels (*27.3% w/ ≥ 75% stenosis*) vs placebo (N=61, 53/137 vessels (*38.7%*); On per-Pt basis, '003 (N=75, 30/75 (*40.0% w/ ≥ 75% stenosis*) vs placebo (N=61, 33/61 (*54.1%*); so, 47/75 = 62.7% vs 53/61 = 86.9% (28% risk reduction), p=0.101; PCE via angiography at 12mFU, wall thickness by IVU/S; Also, 30% relative reduction in composite endpoint (death, failed SVG), p=0.034; Lic'd to *Co.*; Ph 2 PCE was on a *per graft basis and only at 12mFU; Ph 3 are ITT, per-Pt.*; SAE was '003 (12%) vs placebo (16%), not SS;

8/14/02: Ph 3 begins ("Prevent 4") of *'003* (40µM) in CABG; DB-PC (50/50) in 2,400 Pt.s (≥ 2 grafts) at 107 US sites; PCE (90% power for 25% *per Pt.* risk reduction) is % of Pt.s w/ ≥ 75% blockage (angiography) at anytime ≤ *12mFU*; Duke Clinical Research Institute is CRO; Also enrolled 600 Pt.s for 5yFU;

11/18/02: AHA #343: Ph 2b data update ("Prevent 2") Eberhard Grube, for *'003* in CABG; 3-D IVU/S at 12mFU for 65 evaluable as placebo (N=30) vs '003 (N=35); Weak data, e.g., vessel size ↑ in response to intimal accumulation larger (better; *0.5±0.5*) vs placebo (*0.3±0.4*), p≤0.05; Subset analysis...

9/18/03: PR; Ph 3 enrollment done (1st, "Prevent 4") for *'003* in CABG; N=2,400

10/03: Ph 3 enrollment done ("Prevent 5?" extra 600 pt.s) for *'003* in CABG; N=600 w/ 5yFU and PCE of AMI, death, repeat CABG; Post-Approval Confirmatory Trial;

4/27/04: At CIBC Conf.; Prevent 4 (CABG) needs *25% ↓ in failure*; Drug (18.7%) vs placebo (25%); 91% powered even if only 80% get angiographic FU;

Q1/05E: Ph 3 data for *CABG*;

Q2/05E: Submit NDA;

Again, there seems to have been a "rush to Phase 3" by Corgentech, with at least two notable changes, from Phase 2, in the clinical endpoint. First, the German Phase 2 study reported quantitative coronary angiography (qCA) results on a *per vessel* basis. Specifically, occlusion of ≥ 75 percent was considered serious (as appropriate) and was counted as vein graft failure. On a per vessel basis (and including death in the composite endpoint, which appears not to have been significant), the trial met the PCE at p=0.034. However, when the results are calculated on a *per patient* basis, as will be required in the Phase 3 trial, a reduction in vein graft failure of 26 percent was observed, but this was not statistically significant (p=0.101).

The Phase 3 trial requires each patient to receive at least two venous bypass grafts. And, in this trial, if any vessel is occluded by at least 75%, the patient is considered a "failure" on an ITT basis. Thus, the risk of failure is higher in the Phase 3 trial than in the Phase 2 trial, which, as noted above, failed using the Phase 3 criteria.

A second issue, which may work to the Company's advantage, is that the qCA results in the Phase 2 trial were reported at 12mFU. Some patients, though, were admitted before their scheduled 12mFU due to, e.g., angina symptoms. When all patients were evaluated for vein graft failure, i.e., qCA at any time, the relative risk reduction due to '003 was slightly improved versus placebo. In the pivotal Phase 3 trial, all qCA analyses (up to 12mFU) will be included in the ITT population. Although this is not an obvious risk to the success of the Phase 3, it is a change from Phase 2 and, as such, introduces some risk.

The CABG trial completed enrollment last September ahead of the PBG, despite starting later and enrolling more patients. This was due to the larger patient population and the enlisting of more clinical trial sites. Data are not expected this calendar year.

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There is one other near term event (June, July?) expected before the August expiration of the 180-day lockup period. The Company has designed in a Clinical Steering Committee review of only placebo-treated patients (at 12mFU) in the CABG study. By not unblinding any portion of the active treatment cohort ('003), there is no statistical hit against the ITT data set. The purpose of the interim analysis is to ascertain the vein-graft failure incidence rate with placebo. If the rate turns out to be less than 25 percent, an increased enrollment is planned. While clever in its design, this partial analysis is a double-edged sword. If the placebo group is found to have a low incidence rate, the likelihood of '003 treatment success is certainly diminished, since there is less "headroom" with which to demonstrate efficacy. In addition, expanding the trial's enrollment may delay regulatory progress (since both Phase 3 trials are required for NDA submission) and adds further expense with, possibly, no future value.

The Company has also completed enrolling an additional 600 patients as a "post-approval" confirmatory trial in which the PCE is MACE (death, AMI, repeat CABG) at 5yFU. It is possible that these patients could be rolled into the pivotal Phase 3 CABG trial. If the failure rate in the placebo group is roughly 25 percent (as contemplated), there is still no assurance of '003's success given the higher hurdle set for the PCE. Thus, this analysis can result only in no news or bad news.

Finally, it is somewhat surprising how large both Phase 3 trials are compared to their predicate Phase 2 trials. Since treatment with '003 is ex-vivo, the need for a large safety cohort (> 1,500 patient-years of exposure) is significantly mitigated. One cynical explanation may be a lack of confidence by the Company in the drug's effectiveness. The situation is somewhat reminiscent of Regeneron's grossly overpowered Phase 3 trial of Axokine in obesity. Regeneron followed a single Phase 2 trial in 175 patients with a 2,000 patient Phase 3 trial, although safety was an important and legitimate element. In fact, the efficacy observed turned out to be statistically significant, but so much lower than that observed in Phase 2, that Axokine immediately became clinically and commercially useless.

Risk Assessment

- *Experimental Phase 3 Trials* Corgentech has rapidly advanced the clinical development of edifoligide to treat vein-graft failure. The molecule has undergone limited Phase 2 testing in two indications and, for both Phase 3 trials, the PCE has been changed from what was used in Phase 2. Thus, both trials are fundamentally highly experimental. Although PBG and CABG are similar in their use of vein grafts to bypass clogged arteries, the procedures, base failure rates and surgical specialists are very different. Since the single NDA depends on success in both Phase 3 trials, a clinical failure in one is a regulatory failure for both. The FDA might be willing to consider a submission based on stunning results from one trial, but since vein graft failure is not life threatening (no MACE PCE in either trial), such consideration would be highly unusual.

- *Bristol-Myers Squibb Owns Edifoligide* In October 2003, Corgentech signed a $250 million partnering deal with Bristol-Myers Squibb. In doing so, the Company sold over 50 percent of the worldwide profit potential of '003 for all indications. Bristol-Myers' past licensing deals (Imclone) have revealed less than stellar due diligence. Corgentech's willingness to sell its crown jewel is likewise suspect. Corporate partnerships are a staple of the biotechnology industry; however, signing this deal after both Phase 3 trials were fully enrolled and completing an IPO soon thereafter looks suspiciously like selling at the peak.

Further work should include a discussion with a vascular surgeon and a cardiothoracic surgeon to assess each physician's perspective on edifoligide's potential for clinical utility, ease of use and the true patient population risk profile. Additional discussion with a regulatory authority regarding approvals based on a single Phase 3 trial would be valuable.