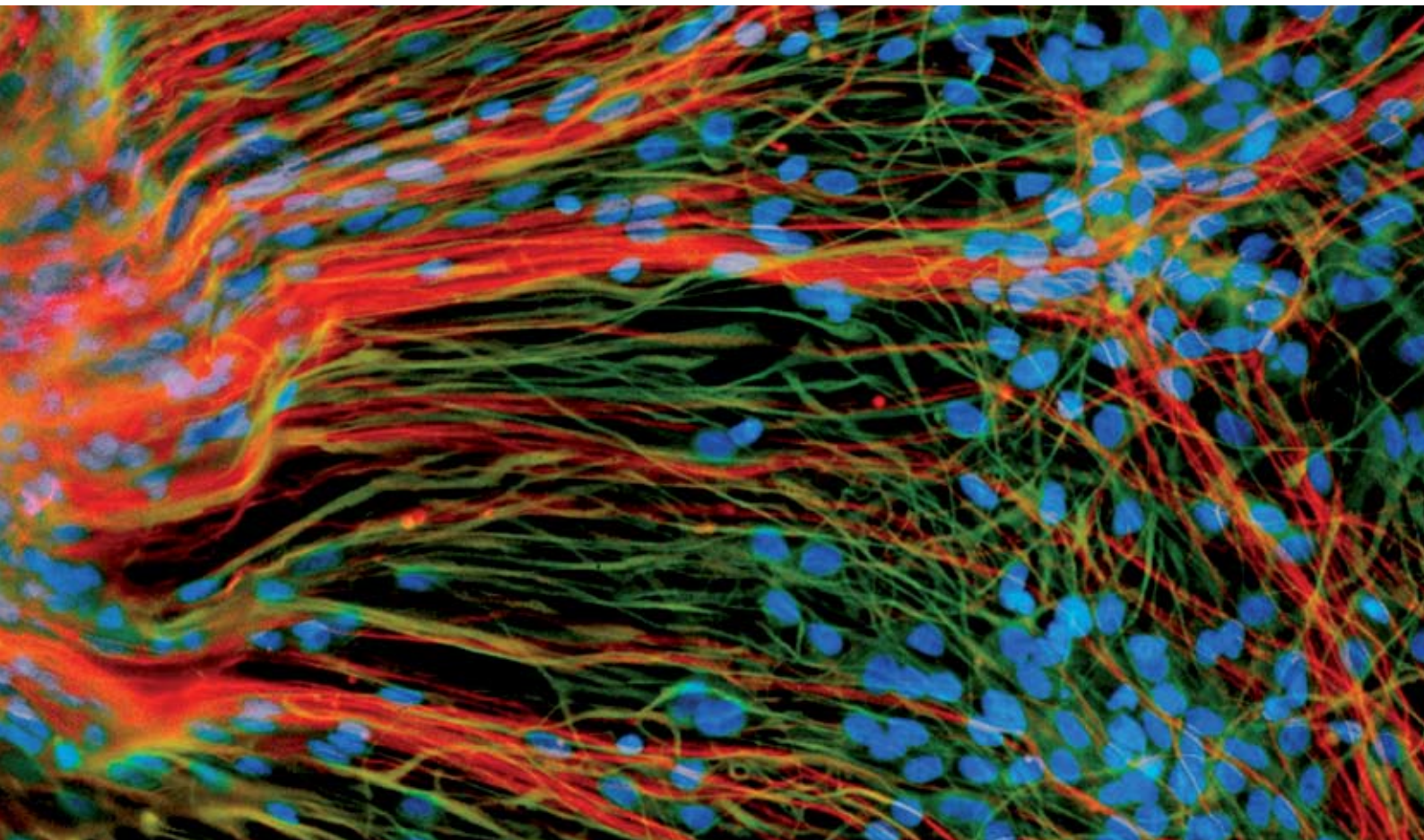


CardioVascular BioTherapeutics Inc.(CVBT)



CardioVascular BioTherapeutics aims to become the first company to develop a viable therapeutic approach based on the formation of new blood vessels, or angiogenesis, using the growth factor FGF-1. Earlier clinical data in 'limited option' heart patients strongly suggest an effect but require definitive trials. The heart applications are significant in their own right but other conditions triggered by vascular disease hold the promise of substantial markets.

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Initiation Report

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I certify that this report represents my own opinions.

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Key Points

19 January, 2007
Price: US\$1.25

Angiogenesis: The Comeback Kid?

CardioVascular BioTherapeutics aims to become the first company to develop a viable therapeutic approach based on the formation of new blood vessels, or angiogenesis, using the growth factor FGF-1. Earlier clinical data in 'limited option' heart patients strongly suggest an effect but require definitive trials. The heart applications are significant in their own right but other conditions triggered by vascular disease promise a substantial market.

- **Cardio angiogenesis lives on!**

Angiogenic therapy is complex: its inability so far to yield persuasive clinical results—whether from proteins, genes or stem cells—has led to scepticism but undiminished passion about its potential. The energies applied to the search attest to the importance of a breakthrough.

- **Messy clinical literature, plethora of opinions**

Clinical investigators are questioning whether single protein or gene agents can be effective in inducing lasting angiogenesis. This leaves the impression that few believe in such a strategy.

- **Cardio's approach is different from previous efforts**

It uses a drug believed to be more potent in heart applications and a delivery mechanism believed to be the most effective.

- **Proprietary or what?**

FGF-1 was one of the first growth factors discovered, so it lacks a composition of matter patent. Even so, barriers do arise out of methods/use or manufacturing IP. In addition, the US and EU regulatory pathways for therapeutic proteins pose additional barriers to entry.

- **Atherosclerosis is a pervasive vascular disease affecting more than the heart**

Other than heart disease, potential candidates for this therapy include sufferers from diabetes, stroke, bone fractures, unhealed wounds, lower back pain and gastrointestinal problems. Markets are in the billions of dollars, if angiogenic therapy can be proven to work.

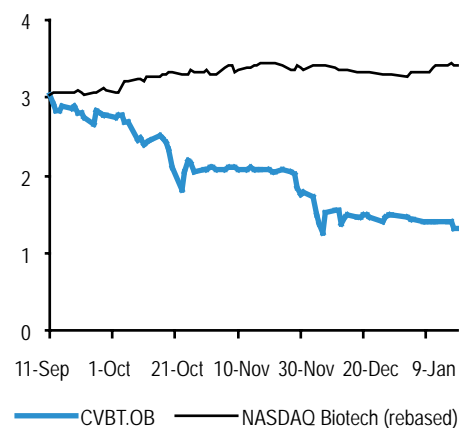
- **The company is in transition from relative obscurity to institutional respectability**

The magnitude of the opportunity is such that it calls for institutional financing and all this entails. The forthcoming AIM listing and associated financing, if successful, would represent the start of this process.

- **Scepticism abounds so the opportunity to uncover hidden value is real**

The next 12-18 months will generate crucial data in FDA sanctioned trials. These hold the potential to reveal whether the pugnacity, perseverance, enthusiasm and passion of the founders of Cardio is misplaced or not.

Price chart (US\$)



Value of Equity

| | |
|---------------------|----------------------|
| Core Scenario | US\$860m |
| Optimistic Scenario | US\$1801m |
| Value per share: | US\$6.94 - US\$14.53 |

Company details

| | |
|---------------------------|---|
| Quote | |
| Shares | |
| -OTC BB | CVBT.OB |
| Hi-Lo last 12-mos. (US\$) | 1.10 - 9.00 |
| Shares issued (m) | 125.5 |
| Fully diluted (m) | 129.7 |
| Market Cap'n (US\$m) | 175.8 |
| Nominated Advisor: | Zimmerman Adams www.zimmint.com |
| Financial PR: | cityProfile www.city-profile.com |
| Website: | www.cvbt.com |

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Overview

CardioVascular BioTherapeutics Inc. (Cardio; CVBT; US, OTCBB) develops therapies for the treatment of cardiac and vascular diseases; based on the administration of fibroblast growth factor-1 (FGF-1 or acidic FGF). **FGF-1** is part of a family of biological growth factors that have been the subject of much investigation for vascular applications. Overall, the field of angiogenic therapy is complex and littered with inconsistencies, confusion and strong clinical opinions.

The jury is still out on the main cardiac indications

The 'limited option' heart patient indication of **CVBT-141a** has major clinical and experimental barriers to overcome. Early data from Germany was strongly indicative and encouraging, but has been subject to divergent interpretations by experts in the field. It still remains possible that this indication might fail on inconclusive statistics. The Phase II protocol attempts to overcome these issues and is the best that can be constructed under the circumstances. This is 'make or break' for this indication, though if the trials are inconclusive the company still has other indications to develop.

Both the wound healing and peripheral artery disease indications look like strong candidates

We see these indications as having a good chance of making it to market. Wound healing was pursued by Merck but was dropped for commercial and strategic reasons. Peripheral artery disease or PAD is also a strong candidate. Success eluded earlier approaches, but is more likely in this instance, given the nature of CVBT-141, its *in vivo* action reported in previous work and the method of delivery. The Phase II protocol should show whether the treatment is efficacious and pave the way for effective commercialisation.

The biological mechanisms underlying FGF-1 point to many other indications

Atherosclerosis is a complex, progressive disease of the vascular system, where tissue repair mechanisms fail, narrowing vessels and restricting blood-flow. The FGF family of growth factors plays a pivotal role in tissue repair. This points the way to many other targets.

With planned fund raising, the company has enough cash to last for eighteen months

The proceeds of the IPO in 2005, the \$20 million convertible in 2006 and the forthcoming AIM listing give Cardio breathing space until mid-2008. It will cost around \$80 million to bring CVBT-141's three indications to market. Our view is that capital-raising on this scale calls for a move from the current shareholder base of angels and 'friends & family' to institutional support. By the end of 2007, there should be enough data on the three lead indications to justify such approaches.

Co-founder Dan Montano has a history

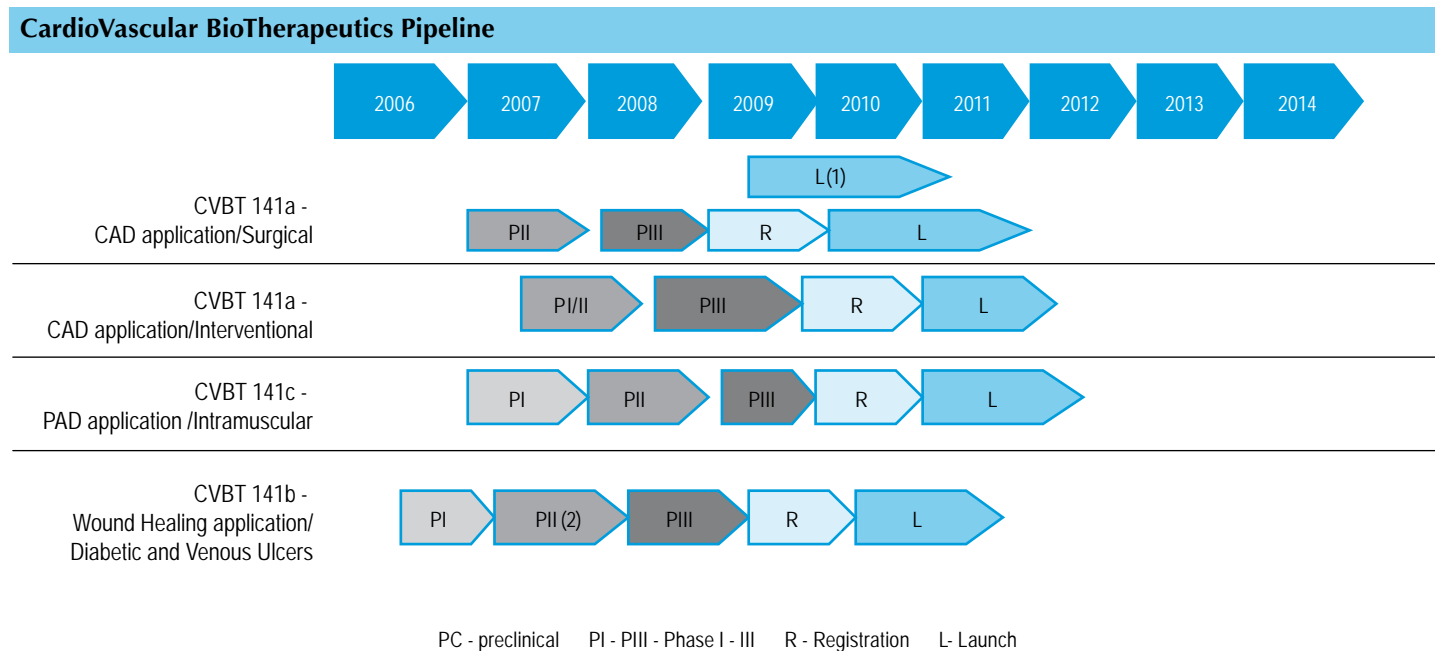
The company's SEC 10K filing contains colour which we have discussed at length with management: we have satisfied ourselves that it is not relevant to the future. The operational team in place has a solid background and is the best guarantee that great value can be obtained for the company's shareholders if some of Cardio's drug candidates hit their desired therapeutic profiles.

The target indications are potentially quasi 'mass market'

The market opportunity available to the front line indications is substantial. Allowing for what we believe are realistic market penetrations for a product for which there are no visible alternatives, our base case suggests a total market opportunity north of \$5 billion. The optimistic case, more in line with Cardio's view of penetration potential, is close to \$12 billion. Although supported by positive animal data in many cases, it is too early to tell whether the company's other projects that are at pre-clinical will lead to viable commercial applications.

However unconventional, the approach is based on credible science

The company's history may appear unusual for the biotech and emerging pharma world, and the clinical angiogenesis literature may be messy, but the differentiated approach and the credibility of the effort are not in question. We believe that this is not a story to ignore. The approach is sound, the objectives seem realistic and while the issue of IP is complex, it may not be insuperable. There are plenty of roadblocks ahead but the potential seems real to us and investors should take note if only to gauge when to jump on the bandwagon.



(1) FDA Expedited Review

(2) Phase I/II

Source: CardioVascular BioTherapeutics, Inc & Objective Capital estimates

Valuation

Valuation rationale

Cardio’s strategy takes a two-pronged approach to the development of its business. On the one hand, it wishes to develop its own sales operation targeting the circa 75 major US heart centres with CVBT-141a and all that this entails by way of G&A, sales & marketing costs. On the other hand, it plans to license out its other products and markets at the latest stage possible so as to maximise royalties. We have therefore applied a mixed valuation methodology whereby:

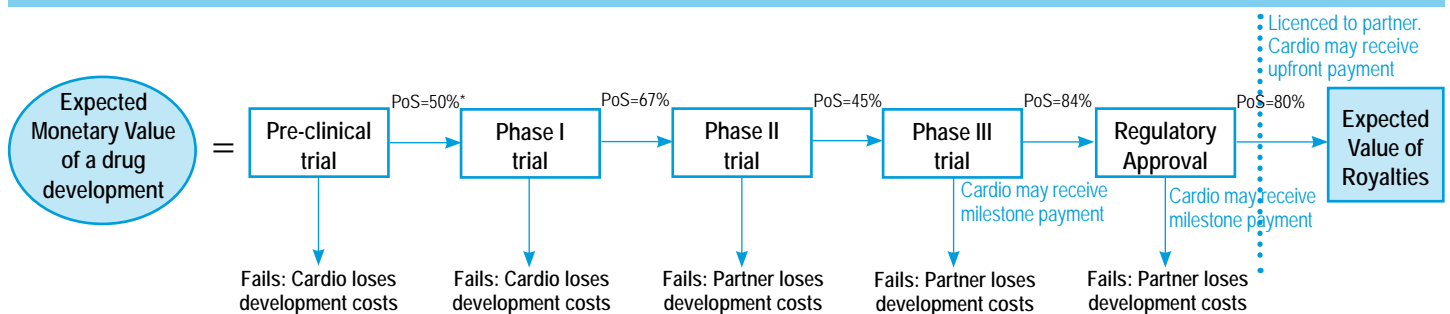
- the US market for CVBT-141a has been valued based on its net revenue in the classic fashion; and
- the licensing streams of other markets and indications are valued separately focusing on the NPV’s of royalty streams.

Angiogenic therapy represents the first quasi ‘mass market’ application of a biotech product. We have only included revenue streams where the stage of development of the product triggers a clear path to revenue. While we have summarised the market potential for the other applications, they are not yet included in our valuation analysis.

We have built two scenarios: a base-case that we believe to be realistic; and a more optimistic case based on the best performance that could be achieved by these products. The latter is more closely aligned with the company’s own view – and not unreasonable if the pipeline fully hits its therapeutic targets. These diseases are major healthcare problems generating extraordinary revenue possibilities. The uniqueness of the present case is that while competition generally limits potential revenue, for the moment, there are few visible competing alternatives leading to unusually large market projections.

The base case values Cardio at around \$6.94 per share. The optimistic case values the shares at \$14.53. This range of expectations is unusually large, reflecting the early stage of the company and the uncertainties inherent in reaching the company’s clinical targets.

Expected Monetary Value of a development drug – licencing model



* industry averages

We have made the following key assumptions:

- **The distribution model remains relatively undefined.** As a consequence, our model is revenue driven, assuming a realistic net margin. The company has licensed selected 'Rest of World' (ROW) territories to KDBC and CPI. It retains an interest in CPI. We assume that this represents no more than 20% of the ROW.
- **The model assumes success with the company's pre-marketing model.** By pre-marketing to opinion leaders in the user community sufficiently early in the process — e.g., Phase II — a rapid ramp-up to maximum penetration can be enabled. Experience suggests that this reduces the ramp-up phase from the usual four to five years by upto two years; we have assumed a three year ramp-up.
- **We assume a rapid take-up by surgeons who perform CABG** in our CAD direct (direct injection through a mini-thoracotomy into the myocardium) revenues if angiogenic therapy is seen to work. However, we have assumed that these will be substantially cannibalised by the introduction of a catheter-based system in circa 2011. We have not included the potential for adjunct angiogenic therapy during CABG procedures where large-vessel disease implies the presence of 'diffuse' disease. Whether surgeons will take up the mantra is unclear at this time. Assuming reimbursement codes are in place, it is certainly plausible that surgeons will perform this procedure 'off label'. This could offer significant upside.
- **Modeling for CAD catheter assumes a rapid take-up.** We assume a market penetration of between 17% and 50%. This finds parallels in balloon angioplasty and stents where even higher levels have been achieved. Even so, pharma products with revenues of between \$5 billion and \$10 billion are rare, prompting caution at this early stage.
- **The size of the PAD market has attracted a number of other approaches** that are potential competitors, but their results have been mixed to date. The 'optimistic' model for PAD assumes a clear therapeutic benefit and the absence of effective competition giving rapid take-up to levels so high as to be a pharma blockbuster.
- **We see wound healing as the indication with the best chance of making it to market.** Even so, our estimates of market penetration are cautious, with Johnson and Johnson's Regranex showing how hard market share can be to come by. Wound treatment is complex: lesions often respond to traditional approaches in the hands of a specialist. In addition, the market is fragmented, with non-closure treatments performed by a variety of physicians, embracing GP's, diabetologists, podiatrists and specialists in wound-care itself. We may be erring on the side of caution, but we feel that the projection of substantial penetration rates awaits a clear market distribution strategy and the demonstration of substantial benefits in terms of time to wound closure.

Expected Value of CAD Direct

| Scenario (\$m) | Core | Optimistic |
|----------------------------------|---------------|---------------|
| EV of Royalties | 2080.4 | 2896.0 |
| Likelihood of success (PoS) | 20% | 20% |
| EMV of Royalties | 416.1 | 579.2 |
| Add: EMV of upfront payments | 0.0 | 4.5 |
| Add: EMV of milestone payments | 0.0 | 0.0 |
| less: EMV of dev costs | 16.1 | 16.1 |
| EMV of CAD per share (\$) | 400.0 | 567.7 |
| | 3.23 | 4.58 |

See page 29 for details

Expected Value CAD Catheter

| Scenario (\$m) | Core | Optimistic |
|----------------------------------|---------------|---------------|
| EV of Royalties | 2016.4 | 5645.5 |
| Likelihood of success (PoS) | 10% | 10% |
| EMV of Royalties | 201.6 | 564.6 |
| Add: EMV of upfront payments | 0.0 | 26.3 |
| Add: EMV of milestone payments | 0.0 | 0.0 |
| less: EMV of dev costs | 6.7 | 6.7 |
| EMV of CAD per share (\$) | 194.9 | 584.2 |
| | 1.57 | 4.71 |

See page 29 for details

Expected Value of PAD

| Scenario (\$m) | Core | Optimistic |
|----------------------------------|---------------|----------------|
| EV of Royalties | 5585.3 | 12785.4 |
| Likelihood of success (PoS) | 10% | 10% |
| EMV of Royalties | 558.5 | 1278.5 |
| Add: EMV of upfront payments | 0.0 | 23.1 |
| Add: EMV of milestone payments | 0.0 | 0.0 |
| less: EMV of dev costs | 6.1 | 6.1 |
| EMV of PAD per share (\$) | 552.4 | 1295.6 |
| | 4.46 | 10.45 |

See page 31 for details

Expected Value of Wound Healing

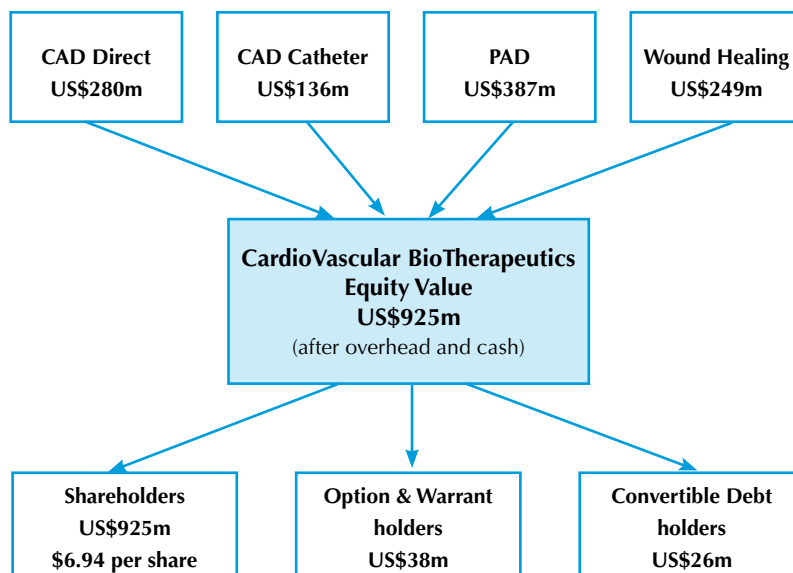
| Scenario (\$m) | Core | Optimistic |
|------------------------------------|---------------|---------------|
| EV of Royalties | 1202.4 | 1588.3 |
| Likelihood of success (PoS) | 30% | 30% |
| EMV of Royalties | 360.7 | 476.5 |
| Add: EMV of upfront payments | 0.0 | 24.2 |
| Add: EMV of milestone payments | 0.0 | 0.0 |
| less: EMV of dev costs | 5.5 | 5.5 |
| EMV of Wound per share (\$) | 355.3 | 495.3 |
| | 2.87 | 4.00 |

See page 35 for details

Valuation Summary (\$m)

| Development drugs | Core | Optimistic |
|-----------------------------------|-------------|--------------|
| CAD | | |
| - Direct | 280 | 397 |
| - Catheter | 136 | 409 |
| Total CAD | 416 | 806 |
| PAD | 387 | 907 |
| Wound Healing | 249 | 347 |
| Overhead | 156 | 156 |
| Expected value of pipeline | 896 | 1904 |
| Add: Starting cash and new funds | 29 | 29 |
| Total Current Value for Firm | 925 | 1933 |
| Less: Bank & Convert Debt | 26 | 40 |
| Total Value to Equity Claims | 899 | 1892 |
| Less: Options | 38 | 91 |
| Ordinary Equity Holders | 860 | 1801 |
| Value per share (\$) | 6.94 | 14.53 |

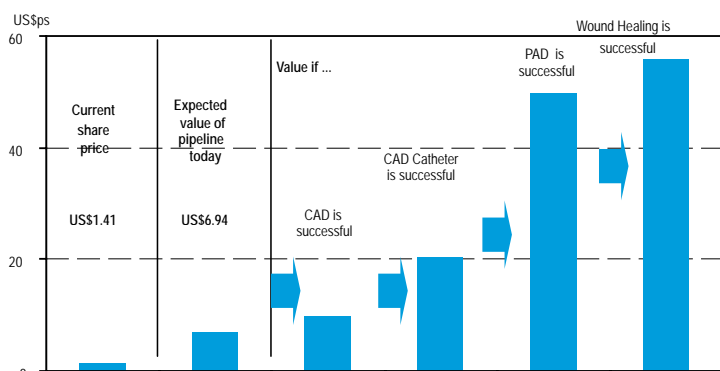
Components of CardioVascular's Entity Value



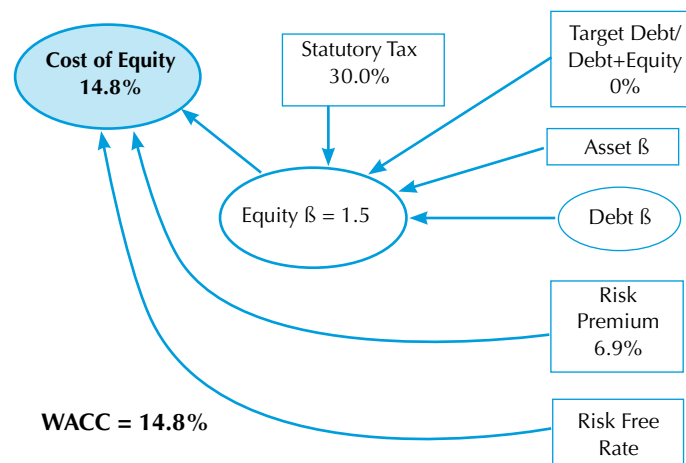
Comparable Company Table

| | Symbol | Market Cap m | Shares Out. mm | Price | Rev Latest | Cash/Equiv latest | Cash/share | Price to cash | Market Cap to Sales | Comment/Partners/Deals |
|--------------------------------|---------------|--------------|----------------|---------|------------|-------------------|------------|---------------|---------------------|---|
| Dollar Zone | | | | | | | | | | |
| CV Therapeutics | CVTX (Nasdaq) | \$797 | 57 | \$14.02 | \$19.0 | \$81.1 | \$1.43 | 9.8 | 42 | Cardiovascular therapeutics |
| Corautus Genetics | VEGF (Nasdaq) | \$7 | 20 | \$0.37 | \$0.1 | \$30.3 | \$1.54 | 0.2 | 91 | Gene therapy company/VEGF-2 trials |
| Cardium Genetics | CDTP (OTCBB) | \$106 | 32 | \$3.35 | \$0.0 | \$11.5 | \$0.36 | 9.2 | NM | Gene for FGF-4/SheringAG/Phase III/ Diabetic Ulcers |
| Endovasc Inc. | EVSC (OTCBB) | \$5 | 160 | \$0.03 | \$0.5 | \$0.0 | \$0.00 | NM | 11 | Owns Angiogenix/treatment for PADIC |
| LifeCore Biomedical | LCBM (Nasdaq) | \$230 | 14 | \$16.91 | \$63.0 | \$26.6 | \$1.96 | 8.6 | 4 | Skin substitutes and other biomaterials |
| United Therapeutics | UTHR (Nasdaq) | \$1,237 | 21 | \$57.58 | \$115.5 | \$27.6 | \$1.29 | 44.7 | 11 | CV therapeutics/cancer/infections |
| Medicure | MCU (AMEX) | \$153 | 116 | \$1.32 | \$0.3 | \$24.3 | \$0.21 | 6.3 | NM | CV drug discovery |
| GenVec | GNVC (Nasdaq) | \$181 | 73 | \$2.47 | \$26.0 | \$25.3 | \$0.34 | 7.2 | 7 | Gene therapy company |
| Average | | | | | | | | 12.3 | 28 | |
| Cardiovascular BioTherapeutics | CVBT (OTCBB) | \$192 | 125 | \$1.54 | \$0 | \$13 | \$0.10 | 14.9 | | |
| GBP Zone | | | | | | | | | | |
| AGI Therapeutics | AGI (AIM) | £76 | 67 | £1.13 | £0.0 | £30.0 | £0.45 | 2.5 | NM | Self develop/specialty pharma |
| Ark Therapeutics | AKT (LSE) | £134 | 171 | £0.78 | £2.4 | £6.3 | £0.04 | 21.2 | 57 | CNS vascular drug development/outlicensing |
| Vernalis | VER (LSE) | £245 | 311 | £0.79 | £14.3 | £40.2 | £0.13 | 6.1 | 17 | Novartis, Endo, Biogen Idec CNS drugs |
| Average | | | | | | | | 10.0 | 37 | |
| Other | | | | | | | | | | |
| AnGes MG Inc | Tokyo | 75,306,295 | 103585 | 727 | 3,000,000 | 30,000,000 | 289.62 | 2.5 | 25 | HGF for PAD/Daiichi Partnership (in Yen 000's) |

Current EMV and value if pipeline is successful (\$ps)



Weighted Cost of Capital



The risk of clinical failure and the inability to take an indication forward

The pipeline ranges from Preclinical to Phase II clinical indications: it is too early to tell which will satisfy the test of statistical significance.

Trial design difficulties in monotherapy 'limited option' CHD patients

Preliminary data seems promising, but the spectre of a placebo effect in such trials looms large and divides the community as to how to detect a 'true' therapeutic effect. It is unethical to perform a mini-thoracotomy combined with an intra-myocardial injection and not offer treatment, so design of the trial is crucial. The intended protocol appears to be the best given the circumstances, although it may still fail to demonstrate a therapeutic effect.

A different delivery system might yield results that are easier to analyse

But the latter is still in the development stage. Percutaneous administration using an intra-cardiac injection catheter into the ischemic area would solve the trial design problem, but the development of such delivery systems remains preclinical and a proof-of-concept trial has yet to be initiated.

Trial design for other indications is easier but barriers remain

Indications such as PAD (Peripheral Artery Disease) and wound healing might be better bets, but it is too early to tell whether they will emerge from clinical development. Other indications are still at the preclinical/ proof-of-concept stage and require clinical data to justify investor attention.

Legacy "sentiment" issues are real

Not all investor will share our attitude towards the colourful past of Cardio and this may limit its ability to raise significant capital. In the end, only meeting the milestones, better communication, an orderly transition to institutional capital and a management structure devoid of perceived conflicts of interests will persuade the doubters.

Sentiment weakened by lack of marketing experience or model

At present, there is no distribution strategy other than a preference for as much control as possible in major markets. While the lack of in-house marketing expertise need not be a problem at this early stage, investors are likely to remain sceptical until someone with the right profile comes in. If properly communicated, some of the pre-market work now under way may offer investors some degree of directional comfort.

...and perceptions of cronyism and nepotism

Having family as employees or consultants need not be a hanging offence: we have met those concerned and satisfied ourselves that they add value. Nonetheless, the practice is frowned upon by professional investors, who may also succumb to perceptions of 'cronyism' and of poor corporate governance at the lack of identifiable independent non-execs with relevant experience.

A 'family & friends' company in transition

Many OTCBB and AIM companies have such a profile early in their operations; it can have advantages in that it creates a loyal investor-base. Nonetheless, the sort of money which Cardio is after, can only come from institutions who will expect professional management throughout, with no scent of conflicts of interest. The company recognises this and is moving in the right direction.

Historical background

The founding of the company now known as CardioVascular BioTherapeutics Inc (referred to below as 'Cardio'), was spurred by clinical trials conducted in the late 1990's by Dr Thomas Stegmann, a cardiovascular surgeon based in Fulda (near Frankfurt, Germany) and at the time a member of the faculty of the University of Marburg. Dan Montano learned of these clinical trials and made contact with Dr Stegmann. The two joined with Dr Wolfgang Priemer, an industry acquaintance of Stegmann, and Grant Gordon, a financial associate of Montano, to found the company in 1998 as CardioVascular Genetic Engineering Inc.

Since then, the founders have taken twists and turns to bring the venture to where it is today. For strategic and financial reasons they sought to develop proprietary methods of manufacturing FGF-1. This took them to a group of Ukrainian scientists who were using bacteriophage to manufacture biological molecules. (Bacteriophage are virus-like particles which grow using the genetic apparatus of bacteria.) Based on this technology a separate entity called Phage Biotechnology Corporation (referred to below as "Phage"), was formed to manufacture FGF-1 and other therapeutically-active biologicals such as interferon, growth hormone and erythropoetin (EPO).

Business objectives

Cardio seeks to develop what the company believes are the many indications where formulations of the active pharmaceutical ingredient, or API, of FGF-1, may display efficacy. Based on the scientific literature, Cardio has identified a number of diseased conditions which appear to derive from the narrowing of arteries and other blood vessels. This restricts blood flow to the body structure (**organs, vertebral disk, skin...etc**) where the disease is triggered. Atherosclerosis, the process that triggers this 'narrowing', is a disease based on the elevation of cholesterol-associated metabolism and by-products. This leads to a cascade of events, resulting in blood vessel wall damage, and hardening and thickening of the wall leading to the increased restriction of blood flow at the site. This condition, which is called **stenosis** of the blood vessel, triggers a variety of diseased conditions. These range from myocardial infarction (commonly known as a **Heart Attack**) and **Congestive Heart Failure/CHF** to **Stroke** (resulting from the blockage of blood flow in the brain), most of which can be fatal or highly debilitating. FGF-1 and other growth factors like it are components of a complex, natural mechanism triggered by damage to a variety of tissues, which goes about repairing faults that have emerged. Cardio seeks to harness this repair mechanism to overcome the stenotic blood restrictions that lead to a variety of diseased conditions in the body.

Corporate development strategy

Traditionally, the products of biotechnology companies are surrounded by a complex web of composition of matter, formulation, application and manufacturing patents, which impart a sense of stability and comfort. Some of the companies that develop such products (e.g. Genentech, Amgen or Biogen amongst others) have evolved into full-blown pharma companies, often by licensing out some of their earlier development products to big Pharma and leveraging the funding received, combined with institutional market financing, to develop their own products to market.

In Cardio's case, the prevalent view, rightly or wrongly, is one of an off-patent product, at least from a composition of matter standpoint. This in turn confers a quasi non-proprietary status on FGF-1 itself although, as in the case of CAD and with the Phage patents, can attain protection through patents covering manufacturing, formulation/delivery or application. In fact, the company has just announced that it has obtained a broad patent on the delivery of FGF-1 directly to the myocardium to induce angiogenesis using any delivery method. It remains to be seen if this broad patent, and such other manufacturing patents as the company may obtain, constitute a sufficient barrier. Nevertheless, the patent portfolio as it stands and any formulation/delivery patents that Cardio may be able to garner, should help to delay the onset of competition.

Cardio may also enjoy protection from an ambiguous act of congress, the Hatch Waxman Act, which fails to define a 'biogeneric' regulatory pathway for biosimilars and the attitude of the FDA towards their bioequivalence. Representative Waxman and Senator Hatch plan legislation to clear up this legislative void, but Cardio believes, and we have confirmed this from other sources, that biodrugs, which are not well-characterised clinical biologics, are unlikely to escape the burden of full clinical trials.

Strategically, the bottom line for Cardio is that US legislation is unlikely to see the light of day before 2009/10. It is also unlikely that the FDA will allow products that are not well characterised clinically to be subject to biogeneric competition from a biosimilar without significant testing. This applies all the more if manufactured in different fashion, as would any competitor to Cardio, given the Phage manufacturing patents. In this light, it may be possible to build a market for the various applications the company has identified without incurring much in the way of competition.

Financing strategy

The company has suggested that it steered clear of venture capitalists to minimise dilution and because its founders had access to alternatives by way of angels and "friends and family". We are of the view that the off-patent nature of FGF-1 would have put off conventional sources of capital in any case. Whatever the explanation, the founders tapped their own network. The results are impressive in that Cardio has raised close to \$60 million since its inception. Of this sum, nearly \$17.5 million was raised through the company's 2005 IPO and \$20 million through a subsequent private convertible offering. We are projecting the need for at least a further \$80 million to get its first products to market, at which point internally generated cashflow would by and large take over as the main source of financing.

Cardio makes no bones of its history or financing

The CFO is Mike Flaa, a former audit partner at KPMG. His zeal for disclosure has ensured that the company's 10K filing with the SEC is a page-turner. The Chairman and CEO is Dan Montano, a successful serial entrepreneur with enough net worth to personally guarantee the \$20 million convertible bond offering. Mr Montano is well-connected, an avowed libertarian and involved in national politics. The 10K discloses that he was censured and fined by the NASD for violations arising out of comments on local TV. He appealed to the SEC who mostly sided with the NASD. Mr Montano may have lost that battle but we don't think it has much bearing on the Cardio story.

Our view on the disclosures

The 10K also discloses a potential SEC violation related to earlier convertible offerings in 2001-2004, which were mostly converted at the IPO. This is not of the company's doing and is unlikely to be material; indeed it need not have been disclosed, but the CFO insisted. The 10K also discloses conflicts of interest arising out of the dual management and overlapping boards of Cardio and Phage. Independent committees intended to ensure the equivalent of arms-length decisions on transactions affecting both companies have dealt with these. Also disclosed is Mr Montano's short-cut personal guarantee of the recent convertible offering; this may be seen as a gutsy move to get things done on a timely basis, also attesting to Mr Montano's confidence that Cardio will pull off at least one large indication. Either he is misguided or a genius; only time will tell.

Management and style are in transition

We believe that the CFO's priority is to transition Cardio's capital raising efforts towards institutional investment. Over the next 12-18 months, the operational management will undergo the transformation required to reflect the emergence of more clinical data and the path to commercialisation. The dual roles of the COO and the CFO in Cardio and its sister company Phage will cease when appropriate. In the meantime, we are satisfied that the potential for conflict of interest between the two companies is dealt with effectively by the structures put in place to deal with it.

Financed and ready to go

The effect of Cardio's steamy past is that the company has been financed with minimal dilution and is ready to move on to the next stage. A team is in place with the skills required to take the company forward over the next 12-18 months. Mr Montano and his CFO have developed precise goal-driven plans, down to the particulars of marketing, reimbursement and the attitude of the Managed Care industry in the US. Given the early stage of the indications being developed, this exercise may be premature; on the other hand, it could shorten back-end costs and timelines, accelerating the ramp up towards commercialisation.

Overview

The underlying disease mechanism that angiogenesis addresses is so pervasive that it triggers a wide variety of diseased states. Growth factors in general and the FGF family in particular appear to have a generalised function throughout the body as part of its natural tissue repair mechanism.

Cardio's use of FGF-1 may seem to make the company a one trick pony, but with that single API, Cardio can access multiple indications through multiple formulations and delivery systems. The number of applications that it can pursue with this one growth factor is extensive. As indicated in the accompanying table, which only addresses some of the potential applications, there is a lot of potential mileage to be had from this one drug. Whether this is realistic, both from a biological and from a therapeutic point of view remains to be seen. The scientific literature is replete with positive animal data on these various applications. Only the test of time and the funds to pursue them will tell us whether these will hold up in humans or not.

Much of the work is being carried out by specialised Contract Research Organisations (CROs) or in collaboration with academic institutions. This means that the company's main job is project management; the COO (Dr Jacobs) and his team are qualified to ensure that these pose few logistical problems. Even so, resources are scarce: priorities have been set to pursue the most credible applications first.

Angiogenesis – a primer

The relevant basics first

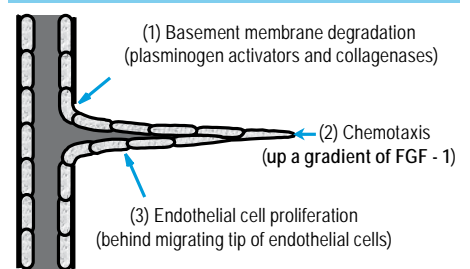
The failures of the past and an assessment of the future can only be understood within the context of the biological mechanisms that underlie this potential therapy.

Angiogenesis is a biological mechanism that triggers the creation of new blood vessels in the body; it is part of an overall mechanism of tissue repair which encompasses the actions of a multitude of growth factors and cellular events.

As seen in the accompanying diagram, angiogenesis involves the creation of a new vessel through a process of cellular proliferation and directional 'sprouting' driven by a gradient of FGF-1.

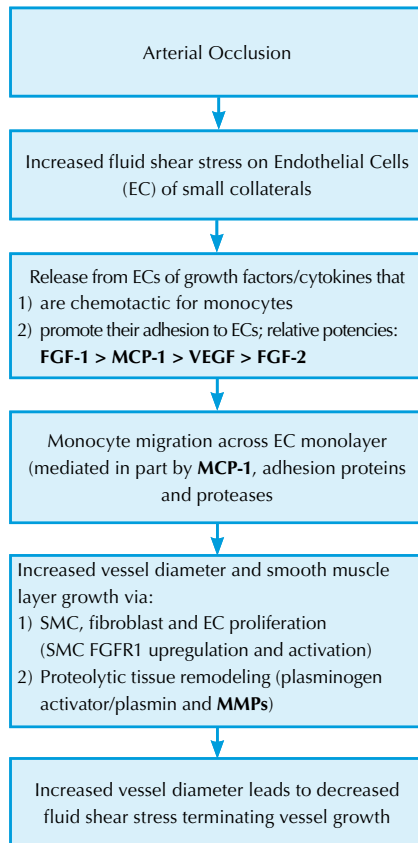
In cardiac and other applications, angiogenesis *per se* is necessary but insufficient for the creation of a durable blood passageway. **Capillaries** (tiny blood vessels or **microvasculature** that are the conduits of blood into any tissue that requires supply to be functional) must be stabilized by **pericytes**, the smooth-muscle cells that reside on its surface. In addition to the growth of capillaries, adequate blood inflow requires the development of larger arteries by a process called **arteriogenesis**, which involves increased luminal diameter (inner diameter of the vessel itself) and the development of the surrounding smooth-muscle cell layers, which increases vessel wall thickness and strength.

Initiation of vessel sprouting



Source: CardioVascular BioTherapeutics, Inc

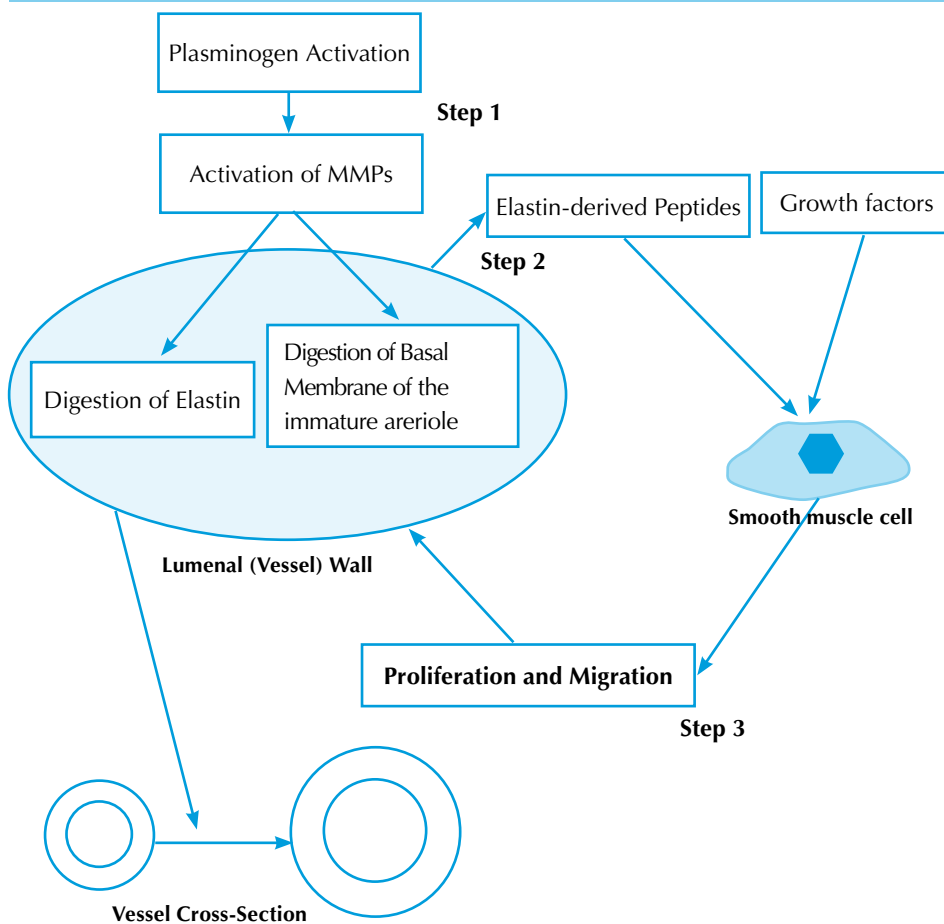
Molecular events leading to Arteriogenesis



Source: CardioVascular BioTherapeutics, Inc, courtesy of Dr Ken Thomas

Arteriogenesis is a multi-step process involving the remodelling and maturation of vessels into a functional blood conduit. It is a complex molecular and cellular process, which is depicted in the accompanying diagram. Whether through naturally occurring arterioles (small arterial vessels) that are a normal part of development, or through **neoangiogenic**¹ arterioles (newly generated ones through angiogenesis), the sheer forces of diverted blood (due to an occlusion) will trigger this process leading to remodelling of the vessel. The second diagram depicts the best understanding that we have found on the process that leads to remodelling, thickening and maturation of the blood vessel wall. This process is a natural mechanism which is believed to be triggered by the forces of blood flow and involves a cascade of events leading to the maturation of the newly-generated vessel and its remodelling to form a fully functional blood conduit to an appropriate tissue.

Enzymatic remodeling of the vessel wall



Source: After Heil, M. & Schaper, W., Circulation Research, 2004;95: p449

¹ Neoangiogenesis is the generation, through angiogenesis of new blood vessels

In simple terms, the binding of growth factors to smooth muscle cells trigger their proliferation and migration, which contributes to the thickening of the vessel wall². This arteriole modelling process is crucial to the building of a lasting blood vessel that can bypass a stenotic occlusion. Without it, angiogenic therapy will fail to generate a functioning vessel to bypass the occlusion. Both FGF-1 and FGF-2 are angiogenic and arteriogenic, but it is thought that the former might be more potent. This family of growth factors appears to be pivotal in this the process, which would explain why arteriogenesis has been observed when they are used.

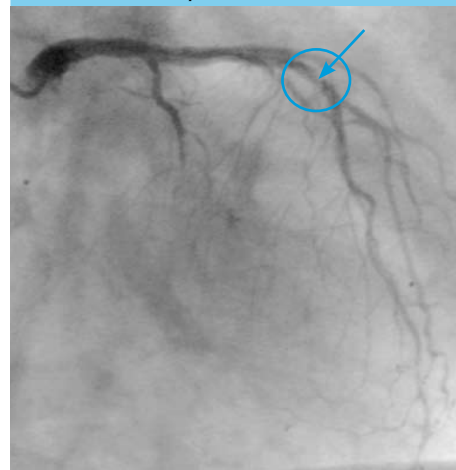
Supported by clinical trials conducted over the past seven years, our discussions with leaders in the field echo Cardio's view that the process of angiogenesis/arteriogenesis is likely to be triggered only by injections directly into the area where damage has occurred. The accompanying top angiogram depicts an example of a narrowed vessel (indicated by the arrow) in what is called diffuse disease (i.e., not in the main vessels) in an x-ray taken after the injection of dye (a procedure called angiography). When an appropriate angiogenic factor is delivered in this way, a demonstrable diffuse blush as seen in the bottom angiogram, which seems to persist even after 3 years. The clinical relevance of this observation remains controversial, for reasons that we address below. A word of caution on this is required. While these angiographically visible blushes establish that angiogenesis has occurred, they do not establish vessel maturation through arteriogenesis; nor that the effect persists to allow improvement in cardiac perfusion. Only functional blood studies using sophisticated imaging technologies such as quantitative perfusion SPECT (which were carried out in the original monotherapy trial in Germany), CT/PET or MRI can actually confirm the functional significance to heart function, through cardiac wall movement, contraction and pumping.

Protein, gene and stem-cell therapy

Many trials have been conducted over the past 8-9 years and the literature is replete with promising preclinical studies, followed by promising dose ranging safety studies, only to be followed by (for the most part) failed Phase II randomised trials. The problem is that these trials use so many protocols, approaches, delivery systems and angiogenic agents as to hamper firm conclusions. The biggest confusion relates to the difference between protein, gene and to a lesser extent stem cell therapies:

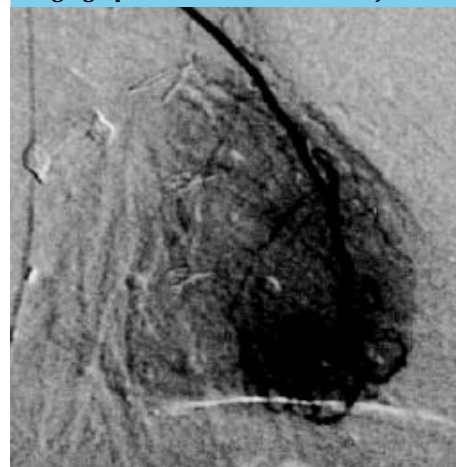
- **Protein therapy** is the direct injection of the underlying protein growth factor, which is a synthetic product of the gene and not the gene itself. The objective is to create a direct causal therapeutic action such as that exerted by insulin in diabetes and EPO in anaemia. Because proteins have short half-lives in tissue, the ability to act is shortened unless the protein acts as a trigger for a cascade or is incorporated into a delivery system. In the case of the FGF's, they are administered bound to heparin (which protects them against degradation) and captured by a cell surface located heparin binding system (called heparan proteoglycans), which enables them to be functionally localized and exert their action.

Diffuse coronary heart disease



Source: CardioVascular BioTherapeutics Inc.

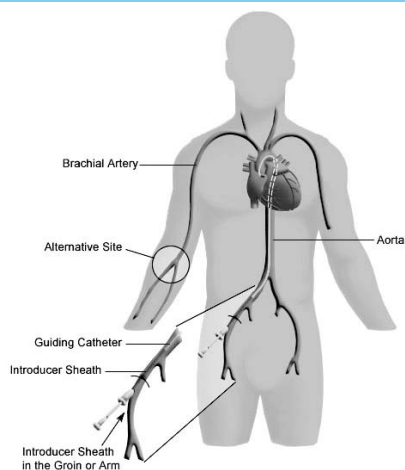
Angiographic 'blush' after FGF-1 injection



Source: Schumacher et al., *Circulation*, 1998; 97: p645-650

² M. Heil and W. Schaper *Circulation Research*. 2004;95:449

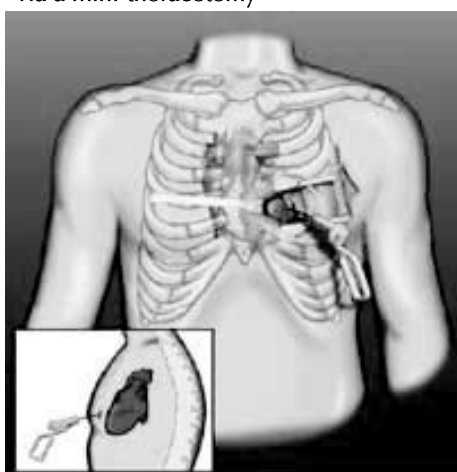
Percutaneous delivery



Source: Akron General Medical Center

Intra-myocardial delivery

via a mini-thoracotomy



Source: Medtronic Inc.

- **Gene therapy** is the therapeutic use of the underlying gene with the objective of introducing it into target cells followed by its expression using the host cell machinery to translate it into protein. This is akin to a virus using a cell to express its proteins and assemble new viruses to expand the infection. In this case it is hoped that the angiogenic factor will be expressed for a significant period of time so as to trigger the desired therapeutic effect.
- **Stem-cell therapy** involves the use of *pluripotent* cells. These have the ability to differentiate into a variety of tissues depending on their location. In cardiac and vascular applications, the objective is that the cell will incorporate into the surrounding tissue, contribute to its function and release the relevant growth factors that begin tissue repair and angiogenic/arteriogenic vessel building. In fact, Stem-Cell Therapy is most likely compatible with the use of growth factors which may be required in order to allow this process to work fully. We feel that these therapeutic approaches might possibly be somewhat ahead of the science.

Dazed and confused delivery

There is a tendency to lump all of the clinical trials under the angiogenic umbrella, but a variety of delivery mechanisms have been employed. These include:

- Intra-myocardial (a form of intra-muscular, straight injection or using a delivery mechanism)
- Intra-pericardial
- Intra-vascular/Intracoronary
- Intra-arterial
- Intra-muscular

Examples of the most relevant (ie, percutaneous intra-myocardial, and via a mini-thoracotomy) are depicted in the accompanying diagrams. Delivery is crucial: results vary widely depending on no more than the mechanism of delivery.

The reason for this bewildering array of delivery mechanisms has more to do with turf battles between interventional cardiologists on the one hand and cardiovascular surgeons on the other, than with underlying science. Nevertheless, percutaneous delivery into the myocardium would be a less invasive and more convenient way of delivering this therapy. To date, the conclusion seems to be that the intravascular and intra-arterial infusions of both proteins and genes often preferred by interventional clinicians is ineffectual and has resulted in side effects at higher doses. The only approach yielding observations of significant or lasting effects is a direct injection into the myocardium. The effects observed using this delivery method in earlier trials will require confirmation in Phase II and Phase III trials before it is seen as a viable therapeutic approach.

The current protocol for direct delivery of FGF-1 into the myocardium requires that the thoracic cage be opened via a mini-thoracotomy. Cardio is developing an alternative protocol, which involves the insertion of an injection catheter into the left cardiac ventricle via a peripheral artery. This percutaneous approach will deliver the drug without the need to open the thoracic cage, which would open up the therapy to a greater number of treatment centres.

Growth factor confusion

Many growth factors are thought to have a role in tissue repair and angiogenesis. A wide variety have been selected for clinical trials including FGF-1 and 2, VEGF (Vascular Endothelial Growth factor), PDGF, GMCSF, HGF and others. VEGF is angiogenic, but appears to lack arteriogenic qualities for cardiovascular and other applications. PDGF and GMCSF involve very narrow mechanisms that have failed to trigger the right kind of effect. HGF has had some success in peripheral arterial occlusions that occur in peripheral arterial disease or PAD.

FGF operates upon the vascular endothelial (inner lining of the blood vessel) and smooth-muscle cells in blood vessels within the heart; gets them to divide; and triggers the necessary arteriogenic mechanisms for tissue remodelling and vessel maturation. In wound healing, FGF harnesses not only angiogenesis but also other processes involving dermal cells (fibroblasts and keratinocytes), which speed up the process of wound repair. FGF-1 has an affinity to all seven of the FGF subclasses of receptors, whereas FGF-2 has an affinity to only five. The two receptors tightly bound by FGF-1 alone are primarily found on epithelial³ tissues, including keratinocytes, which may promote epidermal⁴ repair during dermal wound healing. In addition, one or both of these two receptors have been speculated to be expressed in regions of microvascular branching, consistent with the observation that FGF-1 but not FGF-2 appears to be able to promote the development of branching within the microvasculature. If this is right, they may contribute to angiogenesis. FGF-1 also binds twice as tightly as FGF-2 to FGFR1, the primary FGF receptor supporting vascular endothelial cell mitogenesis (cellular division).

Most of the FGF trials conducted in the last seven years have used FGF-2. These trials were for the most part inconclusive (except for one using an alginate delivery system implanted in the myocardium), but this tells us less about FGF-2's efficacy than about the importance of trial design. The trials failed to show effects which were statistically significant or lasting. The diversity of protocols, delivery mechanisms and vehicles (that is, protein versus gene) make it impossible to draw firm conclusions.

³ Epithelial tissue covers the surface of both the outside and inside of the body is composed of densely packed cells in one or several layers

⁴ The epidermis or epidermal layer is the outermost layer of the skin

The bottom line is that based on previous clinical data, it appears that the intramyocardial and intramuscular routes are the most promising for cardiac and peripheral vascular application respectively. Topical application to open dermal wounds seems to be the only route tested and appears to have encountered some success. There is a plausible biological explanation for this. FGF-1 and -2 do not contain the necessary transport mechanisms to act as an intracellular agent, so it is thought that they are released externally into damaged tissue to exert their effect. This implies that to inject or apply them topically anywhere other than at the site of the injury makes little sense. As we will see later, this forms the basis for the strategy that Cardio will employ in a number of conditions thought to occur as a result of generalised vascular disease driven by atherosclerosis (arterial narrowing resulting from a build-up of intravascular plaque). It is also the basis of a patent that has been issued to Cardio for cardiac therapeutic angiogenic therapy.

Atherosclerosis and human disease

Throughout this primer, we have alluded to cardiovascular, peripheral vascular and other diseases as targets for angiogenic therapeutics. We now turn to the link between them and the reason for the fervour with which angiogenic therapy has been pursued.

Atherosclerosis refers to a condition caused by a highly complex set of biological events, triggered by a variety of genetic, physiological and environmental factors (high cholesterol being the best known culprit). These lead to the narrowing (called stenosis) of arteries and other blood vessels, resulting in progressive restriction of blood flow to a particular tissue or organ.

In CAD (Coronary Artery Disease), the stenoses of coronary arteries can lead to myocardial infarction (heart attack or MI). Equally, more diffuse disease in smaller vessels can lead to MI but also to conditions such as angina pectoris (chest pain) and congestive heart failure (also triggered by cardiomyopathy). As we will see, atherosclerosis is a pervasive vascular condition that has been implicated in a wider variety of diseases from stroke to diabetes, from kidney malfunction, etc.

In addition to the three indications currently in FDA-sanctioned trials, Cardio is planning to pursue a number of promising conditions where some preclinical evidence implicates vascular stenosis as an aetiological factor underlying the diseased state. The accompanying table summarises these applications, potential US patient markets and current status.

Other target applications for FGF-1

| Disease/Condition | Total Pt. Population in millions | Clinical Status | Corroborating Data |
|------------------------------------|-------------------------------------|------------------------|--|
| Lumbar Ischaemia | 26 | Pre-Clinical/PoC trial | Imaging evidence of lumbar-proximal stenoses in the literature. CVBT running 2 PoC human trials. 1 to confirm imaging data and the other to inject FGF-1 into muscle near the stenotic lumbar vessel |
| Post-Stroke Treatment | 6 | Pre-Clinical | Animal studies point to a beneficial effect of FGF-1 post-stroke in sparing brain tissue from further damage |
| Gastro-Intestinal Ischaemia | 1.5 | Pre-Clinical | Animal study evidence of protection against damage after reperfusion of an accutely blocked vessel |
| Kidney Ischaemia | 3 | Pre-Clinical | Similar concept as in GI application aimed at slowing down or reversing the course of renal disease which is though to be caused by atherosclerosis of renal arteries and vessels |
| Femoral Bone Ischaemia/Bone Repair | 1 | Pre-Clinical | Animal studies seem to point to an osteogenic effect of FGF-1 in the bone repair process through the stimulation of new blood supply to the injured area |
| Diabetes | 4.2 | Pre-Clinical | Human evidence of pancreatic artery stenosis and some data on a proliferative effect of FGF-1 in pancreatic islet cells |

Source: Various public sources/CardioVascular BioTherapeutics, Inc

While we have identified competitive technology for each indication, angiogenesis is an active field with many approaches theoretically available. The patents on FGF-1 held by Merck lapsed several years ago. Hence, the potential routes to protection open to Cardio fall under:

- composition of matter
- application/method patents
- manufacturing patents
- orphan drug status
- FGF-1's status as a bio-product
- European 10 year exclusivity for new drugs and devices

Composition of Matter

As FGF-1 is off-patent, an alternate form (such as a modified or mutant form of the growth factor) with significant advantages (stability, potency or other characteristics) would need to be developed to qualify for such a patent. A proprietary delivery system might help, if combined with a solid application/method patent (such as a catheter along with an intra-myocardial injection method patent). Equally, a wound healing formulation that is superior to just a standard formulation might qualify.

Application/Method Patents

If FGF-1 qualifies for any protection, this is where it is most likely to be found, but patents broad enough to be "blocking" are rare. Cardio has just announced the issuance of a patent which covers the intra-myocardial injection of FGF-1 which will offer it full patent protection on both its CAD indications, that is, direct injection through a mini-thoracotomy and a catheter-based delivery system.

A patent-protected, catheter-based system and/or any patent-protected, value-added formulation would help to strengthen proprietary claims, but would need to be impervious to the circumvention, which usually occurs.

Manufacturing Patents

These patents are a similar category to application/method patents and can be useful in preventing others from taking a similar route. The production system developed by Phage was developed to avoid manufacturing bottlenecks prevalent in the field of contract manufacturing and to avoid infringing existing third-party patents. The process is likely to be well protected, although we have not looked at the patents in detail. While they can never be absolutely 'blocking', they can constitute a sufficient barrier to make entry unattractive to others. Phage production does not, in and of itself, constitute a significant barrier as formulations can be produced using other approaches, such as bacterial, mammalian, yeast or baculovirus, if they are cost-effective. Phage's process may turn out only to have significance from a regulatory standpoint, as one more defence against bio-equivalency claims, albeit a weak one in our view.

Orphan Drug Status/Market Exclusivity

If Cardio can find markets where there are less than 200,000 patients afflicted with the disease, they may be able to obtain Orphan drug status, which would trigger 10 years of market exclusivity. Looking at the list of applications being pursued, none has emerged that has that small a market. We are unaware of any other market exclusivity that can be granted to the company.

10 Year Exclusivity in Europe

In the EU, any newly approved drug or indication (patented or not) not previously registered benefits from a 10 year exclusivity period. After 8 years, a generic company can initiate a registration procedure for a bioequivalent drug but will not be able to market it until the 10th year. An additional year related to the time it takes to register a drug is available implying the potential for 11 years of protection. Any new formulation or use patents can serve to extend this up to the allowable timeframe. In the case of biodrugs, the regulatory pathway for a 'biosimilar' have been somewhat clarified. However, this applies only to a relatively restricted class of well characterised biotech drugs.

Bio-Generic Issues

At present, the regulation of bio-generic drugs is a hot topic. The European Union has already moved to generate regulations in this area (Directive 2003/63/EC and two follow-up guidance notes), but barriers (such as immunogenicity testing) still exist and the only product to gain approval to date is Human Growth Hormone (hGH). The EU directive differentiates between simple and complex proteins and has established a graduated level of regulatory requirements proportional to the complexity of the product. But as in the US, the EU regulatory authorities have discretion as to how much regulatory burden they place on the pathway to approval of a product. The products that Cardio are developing, use and manufacturing patents notwithstanding, are not clinically 'well- characterised' and do not fall under the category of products that would be targeted for 'follow-on protein' approval procedures under anything that we have seen or heard about.

What is at stake is the ability to get approval without having to demonstrate bioequivalence and to conduct extensive clinical testing, which run counter to the business and commercial strategies of most generic companies. The commercial opportunity for biogenerics is vast, but it appears that only a few of the therapeutic proteins currently on the market fall under the definition of 'follow on products'. The 'complexity' distinction developed in Europe is also likely to cross the Atlantic. At present, the Hatch-Waxman Act provides for a simple procedure for US companies to demonstrate bioequivalence for chemical-based drugs once a patent expires. The Act sets a statutory timetable for an Abbreviated New Drug Application or ANDA, which gets such drugs approved as generics. The FDA's attitude to 'follow-on products' or biosimilars is outlined in the statement below:

"With small molecule products, there is a long history to support the use of various scientific approaches to establishing "bioequivalence" between products with the same active ingredient(s) product by different manufacturers. We know now that these "bioequivalent" products can indeed be expected to behave in a pharmacologically interchangeable manner when used in patient care. With protein products, as of today, the FDA has not determined how interchangeability can be established for complex proteins."

Source: FDA paper: "U.S. FDA Considerations: Discussion by National Regulatory Authorities with World Health Organization On Possible International Non-proprietary Name (INN) Policies for Biosimilars

Biodrugs are expensive and a significant financial burden to the healthcare system (almost 20% of total healthcare costs in the US): as political pressure builds to bring down therapeutic costs, the tide may slowly be turning. With the Democrats taking over the US Congress hearings and legislation in this area have become more likely. Nonetheless, it is our view that substantial barriers will remain: biogeneric manufacturers are likely to be forced to conduct extensive testing to demonstrate that their product is truly a 'similar' follow-on product which leads us to believe that many will be put off.

Our view is that this may not be relevant for some time for Cardio's pipeline. The recent issuance of the company's use patent on direct injection of FGF-1 in the myocardium may in effect be a blocking patent and could protect all CAD applications (direct injection and catheter-based injection). For wound healing and PAD the application of a 10-year exclusivity will protect in Europe and the test of how 'well characterised' these products are will likely prevail at the FDA. Therefore it may be some time until an 'angiogenic' biosimilar would be allowed to emerge. However, this does not preclude the emergence of a different competitive approach with another factor, gene or stem cells.

As Cardio's FGF-1 is protected by manufacturing patents, any generic competitor would need to circumvent these by producing the product in a different process which would automatically trigger preclinical and clinical testing to demonstrate substantial bioequivalence.

In the end, given the size of the market, a significant business rationale can be built for a biogeneric company to pursue these indications. We do not see such developments as imminent but recognise them as a risk to Cardio's business model unless the company can come up with a proprietary form of the drug that has significant advantages over its current form.

Sales & marketing model

Cardio has not finalised its plans for distribution. This is understandable, given that the company is at least three years away from market. Cardio has a partnership with KBDC linked to an investment that the latter made in the company, and another partnership with an affiliate company, CPI, for various non-major markets, but it is too early to tell how these will be structured. The company retains all rights to the major markets of the US, Japan and Europe, but we believe that it is roughly 18 months away from hiring a VP of sales and marketing. Nevertheless, planning in this area has begun and work on various aspects of sales and marketing has been initiated.

Cardio plans to embrace the modern pre-marketing techniques developed by larger biotechnology companies. When effectively executed, these have accelerated the time to peak sales from a historical average of 4-6 years to only 2-3 years. This will involve conducting an ongoing programme of seminars and demonstrations aimed at creating awareness among 'opinion leaders' at key institutions as early as during the Phase II clinical trials. We concur with this approach and have assumed the impact of this in our forecasts.

Cardio is working with the Bruckner Group (a prominent reimbursement consultant) to explore the economic framework of CVBT-141 and what the company needs to do to ensure that the drug benefits from full reimbursement from both private and public payors. The kind of information collected at clinical trials can be modified to fit the needs of CMS (the Center for Medicare and Medicaid Services who determine Medicare reimbursement), the HMO's and other insurers.

Management recognises that the cost of the drug must satisfy cost/benefit criteria and the reimbursement policy of payors. We believe that Cardio's approach is a well placed nod to the future of the pharma/biotech industry which is at odds with the 'lets charge what the market can bear' approach of many biotechs. The reimbursement problems encountered by some 'novel technology' products are a revealing sign of the future.

CAD/CHF applications

The first indication (chronic refractory CAD/Limited Option - CVBT-141a) is targeted primarily to high volume, major heart centres of which there are around 75 in the US and possibly 200 worldwide. An initial, mini-thoracotomy based procedure would be carried out by a cardiac surgeon. Cardio plans to build a small sales force to tackle this market. A sales force of between 12 and 15 people would be enough for the US; at a cost of between \$3-400k per sales person, which is not out of line with such a large market.

In its discussions with surgeons, Cardio has learned (and so have we) that if CVBT-141a hits its therapeutic profile, (reduction in chest pain for angina, improved stress tolerance for the heart, improved quality of life...etc.), it is likely that this therapy will achieve widespread use in the 280,000 CABG procedures (Coronary Artery Bypass Grafting) performed annually in the US. The principle behind this indication (which we have not included in our analysis at this time) is that where there is large vessel disease (e.g., the coronary arteries) there is almost certainly small vessel/diffuse disease. While it may be difficult to prove the differentiated effect of therapeutic angiogenesis during CABG, should therapeutic angiogenesis become a reality, so will this off-label use.

If and when a catheter system becomes available, the market leaps to roughly 2000 cath labs in the US and a marketing partner becomes a necessity.

This will also lead to a massive shift to this form of therapy away from the mini thoracotomy-based one. Whether the CABG-related administration of this therapy will be enough to sustain the direct open heart indication remains to be seen. The same would be true of the international arena.

PAD

In PAD, the cardiologist, and vascular surgeon are the marketing targets for this procedure. As it is interventional in nature and requires extensive work up and targeting it might also implicate an interventional radiologist who might perform perfusion x-ray MRI and CAT procedures to localise the stenoses to by-pass.

Wound healing

The treatment of non-healing ulcers is the purview of wound healing specialists, specialty clinics, dermatologists and podiatrists. It's an art rather than a science today and involves many steps to insure that the wound closes and to minimise infection at the wound site. Complications lead to amputation and amputation equates to significantly increased mortality rates. The target for this area is clear.

Applications, clinical status and markets

Cardiovascular disease applications

Background

Adjunct to bypass trial: a trailblazer

The original trial published in the journal "Circulation", was trailblazing when it was published, eliciting a favourable comment from the discoverer of angiogenesis Judah Folkman. However, with the passage of time, the data have become controversial. The original trial was an 'adjunct to Coronary Bypass' involving 20 patients treated with CABG and FGF-1 and 20 with CABG and inactivated FGF-1.

Due to the structure of the trial, symptomatic improvements could not necessarily be ascribed to the angiogenic treatment as CABG alone could have triggered them. Nonetheless, an angiogenic blush was seen, persisting at the time of a three-year follow-up. Such persistence is unlikely to be the result of a placebo effect, but its functional and symptomatic significance is unclear due to the nature of the study. All we can say is that this study seems to point towards a mechanistic increase and persistent perfusion in the myocardium resulting from the administration of FGF-1.

Those patients who displayed a significant qualitative improvement in lifestyle continued to do so and certain quantitative measures of improvement persisted but again, these could have resulted from the CABG alone.

Monotherapy trial: strongly indicative and worthy of follow-up

A second open label trial involving monotherapy was conducted and again, patients improved symptomatically and visible angiogenic growth could be seen by dye-perfused angiographic analysis. In this case though, the patients were subjected to exercise testing and monitored using another technique (standard today) called perfusion SPECT (Single Photon Emission Computed Tomography). This analysis shows, using SPECT perfusion, a significant improvement in blood flow after treatment. While the 28% improvement in exercise tolerance observed could have been influenced by a placebo effect, a two fold improvement in blood flow was measured by SPECT. This cannot be solely accounted for by the intra- and inter-patient variability ascribed to this technique by some researchers.

It is now generally believed that pharmacological stress testing is a more reliable measure of heart functionality than exercise stress and in fact the current Phase II in preparation has chosen the latter over exercise stress testing. The company believes (and these arguments are plausible from our point of view) that the SPECT measurements made in the original monotherapy trial, are unlikely to be explained by a placebo effect alone. While this point of view is controversial amongst other clinicians in the field, the Phase II study Cardio plans to conduct is designed to lay this controversy to rest.

Clinical status of 'limited option' patients

'Limited Option' patients with CAD (Coronary Artery Disease) are generally Class III or IV angina patients, who are not candidates for revascularization due to what is called 'diffuse' disease. In other words, the stenoses observed in these patients are present in very small vessels distal to the main arterial vessels (ie, diffuse disease) and are not treatable by Angioplasty or CABG. It is estimated that 15-20% of patients with stable angina (estimated in the US at 6.5 million and 400,000 new patients per annum) are refractory to revascularization. We estimate that, in the US alone, somewhere around 250,000 patients (some estimates go as high as 500,000) that are targets for angiogenic therapy. Other candidate patients can include those who either don't have adequate donor vessels for bypass or have significant stenoses at sites of bifurcation that can't effectively be treated by bypass or PTCA. This category of patients is hard to quantify but would be above and beyond the estimates given above.

Cardio's phase I trial took far too long. There were delays in enrolling patients as the protocol called for joint decisions by the attending cardiovascular surgeon and cardiologist, straightforward in Germany, but presenting challenges in the US. In addition, the FDA required that the company pause to analyse the data after each dosage level. The final results are not yet in, but Cardio's efficient PR machine has made sure that the anecdotal successes of the trial are well covered in the local press.

CAD (direct) revenue assumptions

| Assumptions | 2006A | 2007E | 2008E | 2009E | 2010E | 2011E | 2012E | 2013E | 2014E | 2015E | 2016E | 2017E |
|--|-------|-------|-------|-------|--------------|--------------|---------------|--------------|--------------|--------------|--------------|--------------|
| US market assumptions | | | | | | | | | | | | |
| Patients - Stable angina ('000s) | 400 | | | | | | | | | | | |
| Total patient ('000s) | 300 | | | | | | | | | | | |
| 'Limited option' patients (Chronic CAD+Angina) ('000s) | 300 | 306 | 312 | 318 | 325 | 331 | 338 | 345 | 351 | 359 | 366 | 373 |
| Market share (%) | | | | | 8.0% | 15.0% | 20.0% | 10.0% | 11.0% | 12.0% | 13.0% | 14.0% |
| Number of procedures ('000s) | | | | | 26.0 | 49.7 | 67.6 | 34.5 | 38.7 | 43.0 | 47.5 | 52.2 |
| Revenues | | | | | | | | | | | | |
| (Cost per treatment @ \$9000) (\$m) | | | | | 233.8 | 447.2 | 608.1 | 310.1 | 348.0 | 387.2 | 427.9 | 470.0 |
| Europe market assumptions | | | | | | | | | | | | |
| Patient estimate ('000s) | 270 | 275 | 281 | 287 | 292 | 298 | 304 | 310 | 316 | 323 | 329 | 336 |
| Market share (%) | | | | | | 8.0% | 15.0% | 20.0% | 10.0% | 11.0% | 12.0% | 13.0% |
| Number of procedures ('000s) | | | | | | 23.8 | 45.6 | 62.0 | 31.6 | 35.5 | 39.5 | 43.6 |
| Revenues | | | | | | | | | | | | |
| (Cost per treatment @\$7000) (\$m) | | | | | | 166.9 | 319.3 | 434.2 | 221.4 | 248.5 | 276.5 | 305.5 |
| ROW market assumptions | | | | | | | | | | | | |
| Patient estimate ('000s) | 88 | 89 | 91 | 93 | 95 | 97 | 99 | 101 | 103 | 105 | 107 | 109 |
| Market share (%) | | | | | | 8.0% | 15% | 20% | 10% | 11% | 12% | 13% |
| Number of procedures ('000s) | | | | | | 7.7 | 14.8 | 20.1 | 10.3 | 11.5 | 12.8 | 14.1 |
| Revenues | | | | | | | | | | | | |
| (Cost per treatment @ \$5000) (\$m) | | | | | | 38.6 | 73.9 | 100.5 | 51.3 | 57.5 | 64.0 | 70.7 |
| Total revenues (\$m) | | | | | 233.8 | 652.7 | 1001.3 | 844.9 | 620.7 | 693.2 | 768.3 | 846.2 |

Source: Objective Capital

As this was an 'open label' trial — not randomised and without a control group — caution is called for. A new Phase II protocol, devised to approximate a randomised trial to the extent ethically permissible, is outlined in the appendix.

The main points of comparison are:

- quantitative SPECT perfusion analysis before and after treatment;
- significant differences between patients at a high and low dose;
- the use of pharmacological heart stress tests;
- a comparison to a parallel control group being treated with standard medical care.

While only an approximation of a true placebo-controlled randomised trial protocol, observers contacted believe that this is the best one can do under the circumstances. The key will be the quantitative SPECT analysis under a pharmacological stress test. However, recent discussions with experts in the field of such techniques warn that the intra- and inter-patient variability detected in these patients (particularly under cardiac stress) based on poor spatial resolution and the specificity (its ability to detect blood flow differences as opposed to ischaemia-related damage) of the technology are inherent in its physics.

To be credible, significant alterations (as seen in the original monotherapy trial referred to above in which the SPECT perfusion increased by approximately 100%, i.e. 2-fold, in regions of poor blood flow before treatment) need to be seen for the results to attain credibility. Any difference within the perceived margin of variability (in the 35% range) might be viewed as within the margin of error. Our view from our research is that it might be prudent to run MRI perfusion studies (using CMR) as well in a portion of the patients.

The bottom line is that the Phase II trial should start in the first half of 2007. Some have questioned the ability of Cardio to enrol patients in this trial (based on the experience in the Phase I trial). We accept the company's view that since 25 centres will be running simultaneously and that each one will only need to recruit 4 patients, it should be possible to get this done relatively rapidly. The CRO employed to run this programme has extensive expertise in recruiting CAD patients for such trials. Final analysis will be conducted after 3 months so the trial has a defined series of clinical and time endpoints.

We, and investors by the same token, will have to await the conclusion of this trial to make a judgment on whether this can fly or not. For this group of patients, who endure chest pain just walking across the room, we certainly hope that it does.

Delivery Routes - the future

As mentioned above, ultimately, the success in proving this therapy might hinge on eliminating what is suspected to be a very large placebo effect. To do this may require finding another way to deliver the therapy without having to resort to a surgical procedure. It is nigh on impossible to design a clinical trial protocol that enables, in an ethically acceptable fashion, a true placebo-controlled, double-blind, randomised trial format when a mini thoracotomy is performed (ie, opening up a patient for the sake of doing it is not acceptable). Enter percutaneous delivery via a catheter system in a similar fashion to balloon angioplasty directly into the left ventricle of the heart as depicted in the diagramme on p16. Two designs have been retained and are currently undergoing animal tests for suitability. These devices should be subject to 510K device approval and would be slated to enter human testing sometime towards the end of 2007 or early in 2008.

CAD (catheter) revenue assumptions

| Assumptions | 2006A | 2007E | 2008E | 2009E | 2010E | 2011E | 2012E | 2013E | 2014E | 2015E | 2016E | 2017E | |
|---|-------|-------|-------|-------|-------|-------|-------|-------|-------|--------|--------|--------|--------|
| US market assumptions | | | | | | | | | | | | | |
| Patients - Stable Angina ('000s) | 400 | | | | | | | | | | | | |
| Total patients ('000s) | 300 | | | | | | | | | | | | |
| 'Limited option' patients (Chronic CAD+Angina) ('000s) | 300 | 306 | 312 | 318 | 325 | 331 | 338 | 345 | 351 | 359 | 366 | 373 | |
| Number of Cath labs | 2000 | 2020 | 2040 | 2061 | 2081 | 2102 | 2123 | 2144 | 2166 | 2187 | 2209 | 2231 | |
| Average procedures per cath lab pa | 2000 | 2200 | 2420 | 2662 | 2928 | 3221 | 3543 | 3897 | 4287 | 4716 | 5187 | 5706 | |
| Total Cath procedures ('000s) | 4000 | 4220 | 4460 | 4723 | 5009 | 5323 | 5666 | 6042 | 6453 | 6903 | 7397 | 7938 | |
| Market share (%) | | | | | | 5.0% | 12.0% | 15.0% | 17.0% | 17.0% | 17.0% | 17.0% | |
| Number of procedures (000's) | | | | | | 16.6 | 40.5 | 51.7 | 59.8 | 60.9 | 62.2 | 63.4 | |
| % of total Cath procedures | | | | | | 0.3% | 0.7% | 0.9% | 0.9% | 0.9% | 0.8% | 0.8% | |
| Revenues | | | | | | | | | | | | | |
| (Cost per treatment @ \$9000) (\$m) | | | | | | 149.1 | 364.9 | 465.2 | 537.8 | 548.5 | 559.5 | 570.7 | |
| Europe market assumptions | | | | | | | | | | | | | |
| Patient estimate ('000s) | 270 | 275 | 281 | 287 | 292 | 298 | 304 | 310 | 316 | 323 | 329 | 336 | |
| Market share (%) | | | | | | | 5.0% | 12.0% | 15.0% | 17.0% | 17.0% | 17.0% | |
| Number of procedures (000's) | | | | | | | 15.2 | 37.2 | 47.5 | 54.9 | 56.0 | 57.1 | |
| Revenues | | | | | | | | | | | | | |
| (Cost per treatment @ \$7000) (\$m) | | | | | | | 106.4 | 260.5 | 332.2 | 384.0 | 391.7 | 399.5 | |
| ROW market assumptions | | | | | | | | | | | | | |
| Patient estimate ('000s) | 190 | 193.8 | 197.7 | 201.6 | 205.7 | 209.8 | 214.0 | 218.3 | 222.6 | 227.1 | 231.6 | 236.2 | |
| Market share (%) | | | | | | | | 12.0% | 15.0% | 17.0% | 17.0% | 17.0% | |
| Number of procedures (000's) | | | | | | | | 26.19 | 33.39 | 38.60 | 39.37 | 40.16 | |
| Revenues | | | | | | | | | | | | | |
| (Cost per treatment @ \$5000) (\$m) | | | | | | | | 131 | 167 | 193 | 197 | 201 | |
| Total revenues (\$m) | | | | | | | 149.1 | 471.3 | 856.7 | 1036.9 | 1125.5 | 1148.0 | 1171.0 |

Source: Objective Capital

Competitive Environment

Competition comes in two forms here. Other protein growth factors (such as VEGF-2 or FGF-2 or any combination of these with any others) or other delivery approaches such as the delivery of gene's (in one form or another) underlying these or other factors. An additional approach would be the use of pluripotent cells that are able to differentiate into cells that can trigger the angiogenic process. In CAD, as we mentioned above, the only approach that seems to hint at a viable angiogenic process is through direct delivery into the ischemic (read damaged) muscle of the heart (myocardium).

A series of trials have been conducted using different factors but the most recent have been Gene Therapy-type approaches either using naked DNA or a viral vector (usually Adenovirus). The latest in this series are a set of clinical trials conducted by Corautus Genetics out of San Diego using the gene for VEGF-2 (Vascular Epithelial Growth Factor) in a trial called GENASIS (Genetic Angiogenic Stimulation Investigational Study). This trial aimed to recruit around 400 patients in a Phase IIb protocol involving percutaneous delivery of naked DNA with the VEGF-2 gene using a Boston Scientific catheter directly into the myocardium.

Patient recruitment was halted after 265 patients in April 2006 due to 3 adverse effects (which may have little to do with the treatment) but also because the committee monitoring the trial determined that there was little chance of achieving the primary efficacy endpoint (increased exercise tolerance) of the trial and recommended that patient enrolment be halted. While further analysis will be conducted to determine whether there is any valuable data to be had, there is serious doubt that this approach will yield, anymore than previous trials of this nature have, any significant clinical data.

Most of the current trials that we have been able to find either use gene therapy (combined with G-CSF) to mobilize stem cells for the treatment of Congestive Heart Failure or studies that directly inject Stem Cells into an ischemic area of the myocardium via mapping guided catheter delivery.

A presentation from a group in Hong Kong recently reported at the American College of Cardiology (ACC) the results of a prospective double-blind randomised trial using transplanted autologous (from the patient) Bone Marrow Mononuclear Cells (BM-MNC) implanted using a Noga mapping system in 28 'no hope' patients⁵. The primary endpoint was exercise tolerance. Secondary endpoints included NYHA class, CCS angina class, myocardial function (LVEF) as assessed by MRI, myocardial perfusion as assessed by SPECT, and arrhythmias as assessed by Holter monitoring. In exercise tolerance, the difference before and after as well as between treated patients and placebo at 6 months was statistically significant. In fact the exercise tolerance amongst the placebo group went down 18% over the period while treated patients had exhibited an increase of 20.9%. However, there was no discernable difference in angina class between the two cohorts and while there were differences in myocardial function as assessed by MRI and myocardial perfusion between baseline and 6 month measurements, the differences between placebo and the treated group were not that impressive and look to us to not be statistically significant. Again, it is too early to tell whether this approach can work or not.

⁵ Tse, H-F. et al ACC Annual Meeting (2006) Abstract 422-14

Expected value of Chronic Refractory CAD/Limited Option Indication by direct injection

Summary of Valuation (pre-corp tax)

| Scenario (\$m) | Core | Optimistic |
|--------------------------------|--------------|--------------|
| EV of Royalties | 2080.4 | 2896.0 |
| Likelihood of success (PoS) | 20% | 20% |
| EMV of Royalties | 416.1 | 579.2 |
| Add: EMV of upfront payments | 0.0 | 4.5 |
| Add: EMV of milestone payments | 0.0 | 0.0 |
| less: EMV of dev costs | 16.1 | 16.1 |
| EMV of CAD | 400.0 | 567.7 |
| per share (\$) | 3.23 | 4.58 |

Key Market & Licence Assumptions

| Indication/Market | Route to Market | Royalty Rate/Effective Margin | Impact of Generics | |
|-------------------|-----------------|-------------------------------|--------------------|--------------|
| | | | Approx Date | Price Impact |
| USA | Marketed | 20% | 2030 | -30% |
| Europe | Licenced | 20% | 2030 | -30% |
| ROW | Licenced | 20% | 2030 | -30% |

Sensitivity to change in ...

| Impact of generics (+ % price decline) | -20.0% | -10.0% | +0.0% | +10.0% | +20.0% |
|--|-------------|--------|-------|--------|--------|
| | Value (\$m) | 402.2 | 401.1 | 400.0 | 398.9 |
| Change in Value | 1% | 0% | 0% | 0% | -1% |
| Increase in royalty/margin (+%) | | | | | |
| | -10% | -5% | 0% | 5% | 10% |
| Value (\$m) | 373.0 | 386.5 | 400.0 | 413.5 | 427.0 |
| Change in Value | -7% | -3% | 0% | 3% | 7% |

Components of core valuation (pre-corp tax)

Core Scenario

| Expected Value of Royalties/Revenue (\$ millions) | | | | | |
|---|----------------|----------------------|------------|--------------|-----------|
| Indication/Market | EV of cashflow | Current Stage of Dev | PoS | EMV | % of Val. |
| USA | 1215.6 | Phase 2 | 20% | 243.1 | 12% |
| Europe | 702.2 | Phase 2 | 20% | 140.4 | 7% |
| ROW | 162.6 | Phase 2 | 20% | 32.5 | 2% |
| Total | 2080.4 | | 20% | 416.1 | |

Optimistic view

| Expected Value of Royalties/Revenue (£ millions) | | | | | |
|--|----------------|----------------------|------------|--------------|-----------|
| Indication/Market | EV of cashflow | Current Stage of Dev | PoS | EMV | % of Val. |
| USA | 1674.5 | Phase 2 | 20% | 334.9 | 12% |
| Europe | 991.9 | Phase 2 | 20% | 198.4 | 7% |
| ROW | 229.6 | Phase 2 | 20% | 45.9 | 2% |
| Total | 2896.0 | | 20% | 579.2 | |

Expected Monetary Value of CAD
US\$400m - US\$568m
\$3.23 - \$4.58 per share

EMV of Upfront payments
US\$0

EMV of Milestone Payments
US\$0

Expected value of Chronic Refractory CAD/Limited Option Indication by Catheter delivery

Summary of Valuation (pre-corp tax)

| Scenario (\$m) | Core | Optimistic |
|--------------------------------|--------------|--------------|
| EV of Royalties | 2016.4 | 5645.5 |
| Likelihood of success (PoS) | 10% | 10% |
| EMV of Royalties | 201.6 | 564.6 |
| Add: EMV of upfront payments | 0.0 | 26.3 |
| Add: EMV of milestone payments | 0.0 | 0.0 |
| less: EMV of dev costs | 6.7 | 6.7 |
| EMV of CAD | 194.9 | 584.2 |
| per share (\$) | 1.57 | 4.71 |

Key Market & Licence Assumptions

| Indication/Market | Route to Market | Royalty Rate/Effective Margin | Impact of Generics | |
|-------------------|-----------------|-------------------------------|--------------------|--------------|
| | | | Approx Date | Price Impact |
| USA | Licenced | 20% | 2030 | -30% |
| Europe | Licenced | 20% | 2030 | -30% |
| ROW | Licenced | 20% | 2030 | -30% |

Sensitivity to change in ...

| Impact of generics (+ % price decline) | -20.0% | -10.0% | +0.0% | +10.0% | +20.0% |
|--|-------------|--------|-------|--------|--------|
| | Value (\$m) | 196.4 | 195.7 | 194.9 | 194.1 |
| Change in Value | 1% | 0% | 0% | 0% | -1% |
| Increase in royalty/margin (+%) | | | | | |
| | -10% | -5% | 0% | 5% | 10% |
| Value (\$m) | 176.2 | 185.6 | 194.9 | 204.2 | 213.6 |
| Change in Value | -9% | -5% | 0% | 5% | 10% |

Components of core valuation (pre-corp tax)

Core Scenario

| Expected Value of Royalties/Revenue (\$ millions) | | | | | |
|---|----------------|----------------------|------------|--------------|-----------|
| Indication/Market | EV of cashflow | Current Stage of Dev | PoS | EMV | % of Val. |
| USA | 1096.8 | Phase 1 | 10% | 109.7 | 5% |
| Europe | 626.1 | Phase 1 | 10% | 62.6 | 3% |
| ROW | 293.6 | Phase 1 | 10% | 29.4 | 1% |
| Total | 2016.4 | | 10% | 201.6 | |

Optimistic view

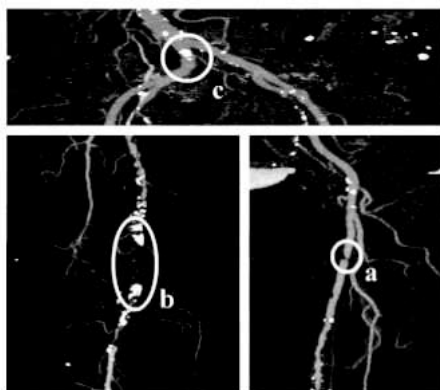
| Expected Value of Royalties/Revenue (£ millions) | | | | | |
|--|----------------|----------------------|------------|--------------|-----------|
| Indication/Market | EV of cashflow | Current Stage of Dev | PoS | EMV | % of Val. |
| USA | 3143.1 | Phase 1 | 10% | 314.3 | 6% |
| Europe | 1790.3 | Phase 1 | 10% | 179.0 | 3% |
| ROW | 713.1 | Phase 1 | 10% | 71.3 | 1% |
| Total | 5646.5 | | 10% | 564.6 | |

Expected Monetary Value of CAD Catheter
US\$195m - US\$584m
\$1.57 - \$4.71 per share

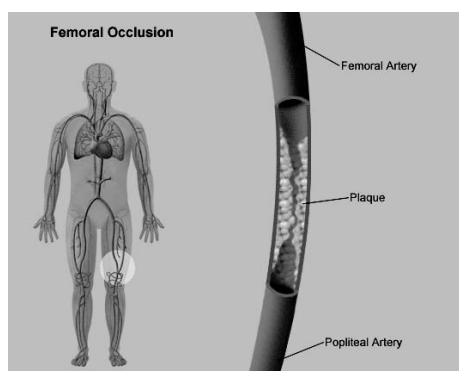
EMV of Upfront payments
US\$0

EMV of Milestone Payments
US\$0

Femoral occlusion



Source: Kanitsar, A et al, *Postprocessing and Visualization of peripheral CTA data in clinical environments*, CESG 2001 meeting



Source: UK HealthCare

Peripheral arterial disease (PAD)

Overview and market

Disease of the peripheral vasculature is common. It can afflict many areas of the body including the cerebrovascular region, the kidney, the intestines and the legs. We focus on disease of the lower extremities, as seen in the accompanying figure and perfusion angiogenic analysis.

Because the majority of those afflicted with this disease are 'asymptomatic' estimates of the population afflicted with the disease vary from a low of 8-12 million in the US all the way to 20 million (The Sage Group). Of these it is estimated that around 3-4 million have intermittent claudication (transient pain) and round 1 million patients with PAD will develop critical limb ischaemia, which almost invariably leads to amputation and a significant increase in mortality. It is estimated that overall, 30% of patients will die at 5 years, rising to 50% at year 10 although from complications elsewhere rather than in the lower extremities. The mortality rate of patients with PAD is second only to bowel cancer (colorectal cancer) and is higher than that for CAD. The manifestations of the disease are transient pain in the legs upon walking (called intermittent claudication) caused by ischaemia. This can be an effect of general atherosclerosis and often afflicts elderly patients (from 70 years on), particularly as a secondary condition in diabetics. It is also a major contributing factor to the development of diabetic foot ulcers, (although not limited to PAD patients with diabetes) a condition that Cardio aims to address with FGF-1 in a separate indication.

Current treatment can include balloon angioplasty (PTA or Percutaneous Transluminal Angioplasty with or without stents) or surgical bypass. However, depending on the size of the vessel in question, PTA may or may not be practical and while in severe disease, grafting is a possible route, it is highly invasive (involving the grafting of a vessel from somewhere else) and would not be as desirable as an angiogenic therapeutic procedure.

Peripheral Artery Disease revenue assumptions

| Assumptions | 2006A | 2007E | 2008E | 2009E | 2010E | 2011E | 2012E | 2013E | 2014E | 2015E | 2016E | 2017E | |
|--|-------|-------|-------|-------|-------|-------|--------|--------|--------|--------|--------|--------|--------|
| US market assumptions | | | | | | | | | | | | | |
| Patients - PAD lower extremities ('000s) | 8000 | | | | | | | | | | | | |
| Patient estimate | | | | | | | | | | | | | |
| (10% with Intermittent Claudication) | 800 | 816 | 832 | 849 | 866 | 883 | 901 | 919 | 937 | 956 | 975 | 995 | |
| Market share (%) | | | | | 3.0% | 8.0% | 15.0% | 16.0% | 17.0% | 17.0% | 17.0% | 17.0% | |
| Number of procedures ('000s) | | | | | 26.0 | 70.7 | 135.1 | 147.0 | 159.3 | 162.5 | 165.8 | 169.1 | |
| Revenue | | | | | | | | | | | | | |
| (Cost per treatment @ \$9000) (\$m) | | | | | 233.8 | 636.0 | 1216.3 | 1323.3 | 1434.1 | 1462.8 | 1044.4 | 1065.3 | |
| European market assumptions | | | | | | | | | | | | | |
| Patient estimate ('000s) | 720 | 734 | 749 | 764 | 779 | 795 | 811 | 827 | 844 | 860 | 878 | 895 | |
| Market share (%) | | | | | | 3.0% | 8.0% | 15.0% | 16.0% | 17.0% | 17.0% | 17.0% | |
| Number of procedures ('000s) | | | | | | 23.8 | 64.9 | 124.1 | 135.0 | 146.3 | 149.2 | 152.2 | |
| Revenue | | | | | | | | | | | | | |
| (Cost per treatment @ \$7000) (\$m) | | | | | | 166.9 | 454.1 | 868.4 | 944.8 | 1024.0 | 1044.4 | 1065.3 | |
| ROW market assumptions | | | | | | | | | | | | | |
| Patient estimate ('000s) | 506 | 516 | 526 | 537 | 548 | 559 | 570 | 581 | 593 | 605 | 617 | 629 | |
| Market share (%) | | | | | | 3.0% | 8.0% | 15.0% | 16.0% | 17.0% | 17.0% | 17.0% | |
| Number of procedures ('000s) | | | | | | 16.8 | 45.6 | 87.2 | 94.9 | 102.8 | 104.9 | 107.0 | |
| Revenue | | | | | | | | | | | | | |
| (Cost per treatment @ \$5000) (\$m) | | | | | | 83.8 | 227.9 | 435.9 | 474.3 | 514.0 | 524.3 | 374.3 | |
| Total revenue (\$m) | | | | | | 233.8 | 886.7 | 1898.3 | 2627.6 | 2853.2 | 3000.8 | 2613.2 | 2505.0 |

Source: Objective Capital

Expected value of PAD Indication

Summary of Valuation (pre-corp tax)

| Scenario (\$m) | Core | Optimistic |
|--------------------------------|---------------|----------------|
| EV of Royalties | 5585.3 | 12785.4 |
| Likelihood of success (PoS) | 10% | 10% |
| EMV of Royalties | 558.5 | 1278.5 |
| Add: EMV of upfront payments | 0.0 | 23.1 |
| Add: EMV of milestone payments | 0.0 | 0.0 |
| less: EMV of dev costs | 6.1 | 6.1 |
| EMV of PAD | 552.4 | 1295.6 |
| per share (\$) | 4.46 | 10.45 |

Key Market & Licence Assumptions

| Indication/Market | Route to Market | Royalty Rate/Effective Margin | Approx Date | Price Impact | Impact of Generics |
|-------------------|-----------------|-------------------------------|-------------|--------------|--------------------|
| USA | Licensed | 20% | 2015 | -30% | |
| Europe | Licensed | 20% | 2020 | -30% | |
| ROW | Licensed | 20% | 2016 | -30% | |

Sensitivity to change in ...

| Impact of generics (+ % price decline) | -20.0% | -10.0% | +0.0% | +10.0% | +20.0% |
|--|-------------|------------|-----------|-----------|------------|
| Value (\$m) | 583.8 | 568.1 | 552.4 | 536.8 | 521.1 |
| Change in Value | 6% | 3% | 0% | -3% | -6% |
| Increase in royalty/margin (+%) | -10% | -5% | 0% | 5% | 10% |
| Value (\$m) | 518.0 | 535.2 | 552.4 | 569.7 | 586.9 |
| Change in Value | -6% | -3% | 0% | 3% | 6% |

Components of core valuation (pre-corp tax)

Core Scenario

| Expected Value of Royalties/Revenue (\$ millions) | | | | | |
|---|----------------|----------------------|------------|--------------|-----------|
| Indication/Market | EV of cashflow | Current Stage of Dev | PoS | EMV | % of Val. |
| USA | 2909.8 | Phase 1 | 10% | 291.0 | 5% |
| Europe | 1818.5 | Phase 1 | 10% | 181.9 | 3% |
| ROW | 857.0 | Phase 1 | 10% | 85.7 | 2% |
| Total | 5585.3 | | 10% | 558.5 | |

Optimistic view

| Expected Value of Royalties/Revenue (\$ millions) | | | | | |
|---|----------------|----------------------|------------|---------------|-----------|
| Indication/Market | EV of cashflow | Current Stage of Dev | PoS | EMV | % of Val. |
| USA | 6682.6 | Phase 1 | 10% | 668.3 | 5% |
| Europe | 4144.3 | Phase 1 | 10% | 414.4 | 3% |
| ROW | 1958.4 | Phase 1 | 10% | 195.8 | 2% |
| Total | 12785.4 | | 10% | 1278.5 | |

Expected Monetary Value of PAD Indication
US\$552m - US\$1296m
\$4.46 - \$10.45 per share

EMV of Upfront payments
US\$0

EMV of Milestone Payments
US\$0

Clinical status

In this case, angiogenic treatment would take the form of direct injection into the ischemic muscle. Improvements will be measured by treadmill exercise, MRI perfusion analysis to detect improvements in blood flow in the afflicted area, if any.

The company will conduct a preliminary phase Ia trial (single dose analysis) using CVBT-141b with patients selected for PAD in the leg with stenoses in arteries of the leg demonstrable by MRI, CT or digital subtraction angiography; and with no other potentially interfering disease points (such as high cholesterol, uncontrolled diabetes or hypertension). The primary endpoint is safety and tolerability, but the trial has been designed to also include exploratory efficacy readouts. Please see the Appendix for a technical summary of the protocol.

Competitive approaches

As with CAD, many attempts have been made inducing neoangiogenesis in intermittent claudication and critical limb ischaemia (CLI) resulting from PAD, which have fallen down in prospective studies. Both FGF-2 protein therapy (Traffic Intra-arterial trial) and VEGF genes have been tested in this indication. The protein therapy (Therapeutic Angiogenesis With Recombinant Fibroblast Growth Factor-2 for Intermittent Claudication or Traffic) trial with intra-arterially injected FGF-2 showed a strong efficacy endpoint measured as a significant increase in walking time after a single dose of FGF-2 in a phase II. The VEGF gene therapy trials, on the other hand, failed to meet statistical significance. A recent trial with Aventis's NV1FGF gene (a non-viral DNA construct licensed from Vical which codes for FGF-1) has just been reported at the ACC last March. The trial, monickered TALISMAN is a multi-centre, prospective trial⁶. The reported study followed up on 107 patients measuring both differences in primary endpoints (healing of ulcers) and secondary endpoints (amputation, death, and ankle brachial index pressure measurements). There were no statistically significant differences in the primary endpoint and none in the secondary endpoints individually. However, amputation and death combined were statistically lower and Sanofi-Aventis have initiated a Phase III trial to investigate this indication. Again, the results are not that clear but at least there is some glimmer of hope. We believe that this data provides further evidence that the ideal conditions for delivering genes to resolve diseased states have not been fully uncovered at this time. However, the fact that treatment with a gene encoding for FGF-1 has displayed some benefits in death rates and amputation may bode well for the direct intra-muscular injection of the protein.

⁶ Nikol, S. et al, *ACC Annual Meeting (2006) Abstract 405-10*

Wound healing

Market overview

The treatment of deep wounds such as decubitus (pressure), venous or diabetic ulcers is one of the most important objectives of modern medicine. Treatments abound and the pipeline of new approaches is extensive, but clinicians await a fully satisfactory treatment. The biology of wounds is depicted in the accompanying diagram. The tissue-repair mechanism causing wound closure arises out of a cascade of biological events. FGF is one of the triggers for this cascade. A fibrin clot covers the wound but FGF (and other agents such as VEGF) brings blood-flow to the area so that repair occurs. In some patients, this fails. Preliminary data seem to confirm that exogenous FGF-1 can aid the process. In contrast to VEGF, FGF also promotes the proliferation of fibroblasts and keratinocytes, which are needed to create new dermal and epidermal tissue.

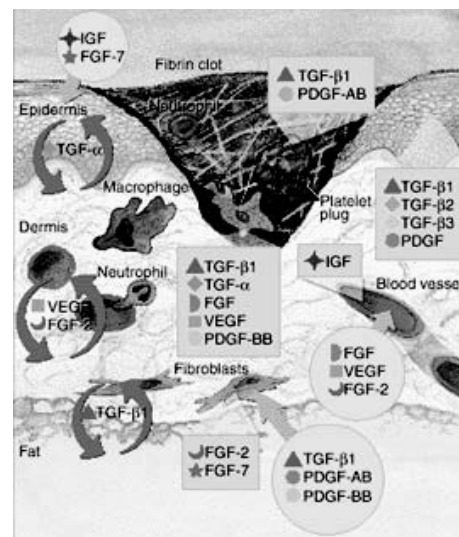
Using standard technology, wounds of this kind can heal within about 20 weeks. Some of the new therapies aim to reduce this period, with the best reported ranging from four to six weeks. Some wounds simply do not heal over this period, requiring care and therapy to achieve closure.

In the past 15 years, several products have been introduced to close non-healing wounds. These have included Apligraf (Novartis), Dermagraft (formerly of Smith and Nephew) and Regranex (Johnson & Johnson). Apligraf and Dermagraft are bioengineered skin products, which contain cellular material: fibroblasts and keratinocytes in the case of Apligraf; fibroblasts in the case of Dermagraft; and a gel formulation of PDGF or platelet-derived growth factor in the case of Regranex.

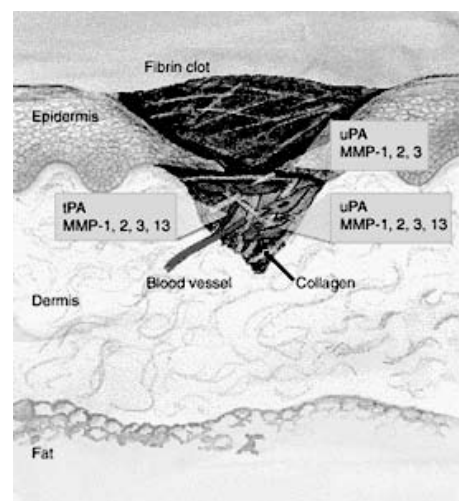
These products appear to achieve satisfactory wound closure for subcategories of patients with refractory neuropathic or diabetic lower extremity ulcers but their cost, ease of application and reimbursement has limited their market success. Only specialised clinics or a limited number of specialists are set up both to use these products effectively and to get them reimbursed. Our discussions with specialists in the field indicate that when a patient presents with one of these wounds it is because they are already considered to display a 'non-healing' prognosis. Nevertheless, specialists will attempt to treat these wounds with standard care to satisfy themselves that the wound will not heal. Many will then switch to an 'advanced' care product such as Regranex or Apligraf. One such specialist indicated that in his clinic, Regranex is the first line of treatment. The progress of the wound is then followed for a period of 2-4 weeks. If no progress is seen, the patient is then switched to Apligraf as a second line treatment. In their hands, they have good success with these treatments but would welcome a product that speeds up the healing process further.

Biological mechanisms

Molecular Cascades



Wound closure mechanics



Source: Sharon Wahl, PhD; *Cytokines in Wound Healing*; The Science Advisory Board

Apligraf has a shelf life of 10 days and costs about \$1200 on an outpatient basis. It is used by specialists but will generally not be used as a first line treatment due to its shelf life profile.

Dermagraft is also an engineered skin substitute but suffers from similar problems to those displayed by Apligraf. Although its shelf life is far longer, it seems to lack the efficacy of Apligraf which some specialists ascribe to the lack of keratinocytes. This product encounters the same difficulties in attracting reimbursement, which only specialised wound healing specialist centres appear to be equipped to deal with. This has limited its market appeal and ultimately the product was discontinued by its licensee Smith & Nephew and sold on to a new company who are preparing to re-launch.

Regranex is complicated to apply and achieves statistically significant wound closure only after 20 weeks. It costs \$500 for a 15 mg tube lasting two weeks or so, bringing the cost of a complete course of treatment to \$5,000. Again, it only finds favour with those centres that are skilled in its use. These centres have indicated to us that they are able to heal a wound with the use of only 2-4 tubes of the product. Reimbursement for Regranex also occurs only with difficulty, so the product has achieved only limited market success.

VAC™ (Kinetic Concepts Inc.) addresses decubitus ulcers, that is pressure-related wounds best known as bedsores. This is the most successful product in wound-care, the market leader with \$800 million in revenues. Its method of operation is obscure, but it is thought that it uses a hyperbaric, negative-pressure treatment to relieve pressure, making for speedier healing.

It is estimated that in the US, there are around 400,000 patients with diabetic foot ulcers (2% to 2.5% incidence) we assume 300-400,000 patients. In addition, the incidence of venous leg ulcers in the US is 0.78% (of the population over 60 years of age), that is some 600,000 patients (some say as high as 2.5 million of the entire adult population). In other words, it would be reasonable to assume that there are at least 1 million patients afflicted with these diseases which could be targets for FGF-1 base wound therapy.

Wound healing revenue assumptions

| Assumptions | 2006A | 2007E | 2008E | 2009E | 2010E | 2011E | 2012E | 2013E | 2014E | 2015E | 2016E | 2017E | |
|---|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| US market assumptions | | | | | | | | | | | | | |
| Diabetic ulcers & venous ulcers ('000s) | 5000 | | | | | | | | | | | | |
| Patent estimate | | | | | | | | | | | | | |
| (10% with non healing) ('000s) | 1000 | 1020 | 1040 | 1061 | 1082 | 1104 | 1126 | 1149 | 1172 | 1195 | 1219 | 1243 | |
| Market share (%) | | | | | 1.0% | 5.0% | 10.0% | 12.0% | 13.0% | 14.0% | 15.0% | 15.0% | |
| Number of procedures ('000s) | | | | | 10.8 | 55.2 | 112.6 | 137.8 | 152.3 | 167.3 | 182.8 | 186.5 | |
| Revenues | | | | | | | | | | | | | |
| (Cost per treatment @ \$2000) (\$m)* | | | | | 21.6 | 110.4 | 225.2 | 275.7 | 304.6 | 334.6 | 365.7 | 373.0 | |
| Europe market assumptions | | | | | | | | | | | | | |
| Patient estimate ('000s) | 900 | 918 | 936 | 955 | 974 | 994 | 1014 | 1034 | 1054 | 1076 | 1097 | 1119 | |
| Market share (%) | | | | | | 1.0% | 5.0% | 10.0% | 12.0% | 13.0% | 14.0% | 15.0% | |
| Number of procedures ('000s) | | | | | | 9.9 | 50.7 | 103.4 | 126.5 | 139.8 | 153.6 | 167.9 | |
| Revenues | | | | | | | | | | | | | |
| (Cost per treatment @ \$1500) (\$m)* | | | | | | 14.9 | 76.0 | 155.1 | 189.8 | 209.7 | 230.4 | 251.8 | |
| ROW market assumptions | | | | | | | | | | | | | |
| Patient estimate ('000s) | 633 | 646 | 659 | 672 | 685 | 699 | 713 | 727 | 742 | 756 | 772 | 787 | |
| Market share (%) | | | | | | | 1.0% | 5.0% | 10.0% | 12.0% | 13.0% | 14.0% | |
| Number of procedures ('000s) | | | | | | | 7.0 | 35.6 | 72.7 | 89.0 | 98.3 | 108.0 | |
| Revenues | | | | | | | | | | | | | |
| (Cost per treatment @ \$1000) (\$m)* | | | | | | | 7.0 | 35.6 | 72.7 | 89.0 | 98.3 | 108.0 | |
| Total revenues (\$m) | | | | | | 21.6 | 125.3 | 308.2 | 466.4 | 567.2 | 633.4 | 694.4 | 732.8 |

Source: Objective Capital

Expected Value of Wound Healing Indication

Summary of Valuation (pre-corp tax)

| Scenario (\$m) | Core | Optimistic |
|--------------------------------|---------------|---------------|
| EV of Royalties | 1202.4 | 1588.3 |
| Likelihood of success (PoS) | 30% | 30% |
| EMV of Royalties | 360.7 | 476.5 |
| Add: EMV of upfront payments | 0.0 | 24.2 |
| Add: EMV of milestone payments | 0.0 | 0.0 |
| less: EMV of dev costs | 5.5 | 5.5 |
| EMV of Wound | 355.3 | 495.3 |
| per share (\$) | 2.87 | 4.00 |

Key Market & Licence Assumptions

| Indication/Market | Route to Market | Royalty Rate/Effective Margin | Impact of Generics | |
|-------------------|-----------------|-------------------------------|--------------------|--------------|
| | | | Approx Date | Price Impact |
| USA | Licensed | 25% | 2018 | -30% |
| Europe | Licensed | 25% | 2020 | -30% |
| ROW | Licensed | 25% | 2018 | -30% |

Sensitivity to change in ...

| Impact of generics (+ % price decline) | -20.0% | -10.0% | +0.0% | +10.0% | +20.0% |
|--|-------------|--------|-------|--------|--------|
| | Value (\$m) | 368.9 | 362.1 | 355.3 | 348.4 |
| Change in Value | 4% | 2% | 0% | -2% | -4% |
| Increase in royalty/margin (+%) | -10% | -5% | 0% | 5% | 10% |
| | Value (\$m) | 329.4 | 342.3 | 355.3 | 368.2 |
| Change in Value | -7% | -4% | 0% | 4% | 7% |

Components of core valuation (pre-corp tax)

Core Scenario

| Expected Value of Royalties/Revenue (\$ millions) | | | | |
|---|----------------|----------------------|------------|---------------|
| Indication/Market | EV of cashflow | Current Stage of Dev | PoS | % of EMV Val. |
| USA | 685.4 | Phase 1 | 30% | 205.6 17% |
| Europe | 382.8 | Phase 1 | 30% | 114.8 10% |
| ROW | 134.2 | Phase 1 | 30% | 40.3 3% |
| Total | 1202.4 | | 30% | 360.7 |

Optimistic view

| Expected Value of Royalties/Revenue (£ millions) | | | | |
|--|----------------|----------------------|------------|---------------|
| Indication/Market | EV of cashflow | Current Stage of Dev | PoS | % of EMV Val. |
| USA | 897.8 | Phase 1 | 30% | 269.3 17% |
| Europe | 506.0 | Phase 1 | 30% | 151.8 10% |
| ROW | 184.5 | Phase 1 | 30% | 55.4 3% |
| Total | 1588.3 | | 30% | 476.5 |

Expected Monetary Value of Wound Healing Indication
US\$355m - US\$495m
\$2.87 - \$4.00 per share

EMV of Upfront payments
US\$0

EMV of Milestone Payments
US\$0

Clinical status

In 2005, Cardio's Investigational New Drug application (IND) to test CVBT-141c for dermal diabetic and venous ulcers was approved. The company is conducting an initial phase Ia single-dose trial that will test eight patients at two dose levels. The protocol is summarised in the accompanying appendix. Once the trial is concluded, a phase Ib or IIa trial will be conducted on 32 patients. This should lead to a phase IIb trial in 2007 and a phase III trial in 2008/9 with launch in 2010.

Competitive environment

There are a wide variety of treatments that are aimed at this market (see appendix for a partial list of those along with their general pros and cons). They fall into the general category of biological and skin substitutes and come in four different formats:

- Biologicals (natural skin)-cutaneous allografts, xenografts and amniotic membranes
- Skin Substitutes-bilayers and collagen-based
- Collagen-based Dermal Analogues-De-epithelialised allograft
- Culture-derived Tissue (see accompanying tables)

The main commercial products that we understand to have significant market presence other than the low cost, dressing and wound healing management approach are:

- Vac™ (Kinetic Concepts Inc.) - hyperbaric negative pressure treatment (\$800 million product)
- GraftJacket/Alloderm (Wright Medical/LifeCell) - (\$150 million estimated)
- Apligraf (Novartis) - cultured fibroblast/Keratinocytes from neonatal foreskin
- Regranex (Jn) - PDGF-based Gel

Cardio's approach will be measured against these, excluding Vac. The target profile is an accelerated rate of healing which would reduce the overall cost of patient management and treatment. The associated cost of care for diabetic foot ulcers has been estimated at between \$10,000 and \$60,000 per annum. The cost of treatment was estimated at around \$5,000 per ulcer episode in 1998 but must be much higher today. Hence the case to be made is part therapeutic, part economic and will depend wholly on the ability to convince both private and public payors of the cost-effectiveness of the treatment.

It is too early to tell what profile FGF-1 will have in this indication but earlier work suggests that this indication might be very effective. Whether it can achieve a therapeutic and economic profile that enables its success remains to be seen.

Other indications

Atherosclerosis is a general vascular disease affecting many areas and possibly the source of a number of human diseases. Although supported by animal studies or limited diagnostic imaging data in humans the indications being pursued are still at what one might call the conceptual stage. Therefore, it is premature to attempt to go through all of them at this time.

The principle behind all of these applications is roughly the same. Atherosclerotic plaque accumulates, a narrowing of a vessel occurs restricting blood flow, the tissue served by the vessel incurs damage, and a diseased state is triggered.

What could be simpler and what could be more devastating in most cases?

The table on p18 lists those that the company is pursuing in either pre-clinical or proof of concept human trials at this time.

Financials

| Profit and Loss | | | | | | | |
|-------------------------------|-------------|--------------|--------------|--------------|--------------|--------------|-------------|
| 31 Dec, US\$m | 2004A | 2005A | 2006E | 2007F | 2008F | 2009F | 2010F |
| Revenue | | | | | | | |
| - Net revenue | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 98.9 |
| - Upfront/milestone payments | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Total | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 98.9 |
| Operating Expenses | | | | | | | |
| R&D | 2.5 | 3.1 | 6.9 | 13.5 | 29.5 | 21.5 | 16.0 |
| SG&A | 2.3 | 8.0 | 11.6 | 12.8 | 14.0 | 15.4 | 17.0 |
| Total | 4.9 | 11.1 | 18.5 | 26.3 | 43.5 | 36.9 | 33.0 |
| EBIT | -4.9 | -11.1 | -18.5 | -26.3 | -43.5 | -36.9 | 66.0 |
| Other & Interest Income (net) | | | | | | | |
| Net Interest Income | -3.1 | -1.3 | -5.2 | -1.7 | -2.2 | -3.6 | -1.4 |
| Adj. Derivatives fair value | 0.0 | 0.0 | 10.2 | -10.2 | 0.0 | 0.0 | 0.0 |
| Net Other Income | -3.1 | -1.3 | 5.0 | -11.9 | -2.2 | -3.6 | -1.4 |
| EBIT | -8.0 | -12.4 | -13.5 | -38.1 | -45.7 | -40.5 | 64.6 |
| Taxes | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Profit after tax | -8.0 | -12.4 | -13.5 | -38.1 | -45.7 | -40.5 | 64.6 |

| Balance Sheet | | | | | | | |
|--|-------|-------|-------|-------|--------|--------|--------|
| 31 Dec, US\$m | 2004A | 2005A | 2006E | 2007F | 2008F | 2009F | 2010F |
| Current Assets | | | | | | | |
| Cash & Equivalents | 4.5 | 8.7 | 8.5 | -19.0 | -64.5 | -105.0 | -40.4 |
| Short term Investments | 0.1 | 0.1 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 |
| Prepaid and other | 0.5 | 0.4 | 1.3 | 1.1 | 1.8 | 1.5 | 1.3 |
| Total | 5.1 | 9.3 | 10.0 | -17.8 | -62.5 | -103.3 | -38.8 |
| Property & Equipment | | | | | | | |
| Deferred Offering fees | 0.0 | 0.2 | 0.9 | 0.9 | 0.9 | 1.0 | 1.0 |
| Other assets | 1.6 | 0.0 | 1.4 | 0.5 | 0.0 | 0.0 | 0.0 |
| Total Assets | 0.0 | 0.0 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |
| 1.6 | 0.2 | 2.3 | 1.4 | 1.0 | 1.0 | 1.0 | 1.1 |
| Liabilities and Stockholders Equity | | | | | | | |
| Accounts Payable | 0.7 | 0.2 | 0.6 | 0.9 | 1.4 | 1.2 | 1.1 |
| Accrued Payroll and Payroll taxes | 0.0 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |
| Other | 2.7 | 0.0 | 0.8 | 0.0 | 0.0 | 0.0 | 0.0 |
| Total Current Liabilities | 3.5 | 0.3 | 1.5 | 1.0 | 1.5 | 1.3 | 1.2 |
| Convertible notes Payble | 8.6 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Convertible notes and embedded derivatives | 0.0 | 0.0 | 11.4 | 3.4 | 3.4 | 3.4 | 3.4 |
| Total Liabilities | 12.1 | 0.3 | 12.9 | 4.4 | 4.9 | 4.7 | 4.6 |
| Stockholders' Equity (deficit) | | | | | | | |
| Common Stock | 11.4 | 38.3 | 42.2 | 59.9 | 59.9 | 59.9 | 59.9 |
| Deficit accumulated | -16.8 | -29.2 | -42.7 | -80.8 | -126.5 | -167.1 | -102.5 |
| Total Stockholders' Equity (deficit) | -5.4 | 9.2 | -0.5 | -20.8 | -66.6 | -107.1 | -42.5 |
| Total Liabilities and Stockholders' Equity | 6.7 | 9.5 | 12.4 | -16.5 | -61.6 | -102.4 | -37.9 |

| Cashflow* | | | | | | | |
|--|-------|-------|-------|-------|-------|--------|-------|
| 31 Dec, US\$m | 2004A | 2005A | 2006E | 2007F | 2008F | 2009F | 2010F |
| Net Loss | -8.0 | -12.4 | -13.5 | -38.1 | -45.7 | -40.5 | 64.6 |
| Depreciation | 0.0 | 0.0 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 |
| Amortization | 2.4 | 1.4 | 0.5 | 0.9 | 0.5 | 0.0 | 0.0 |
| Options & warrants issued for services rendered | 0.1 | 1.8 | 1.6 | 0.0 | 0.0 | 0.0 | 0.0 |
| Adj to derivative fair value | 0.0 | 0.0 | -6.8 | 10.2 | 0.0 | 0.0 | 0.0 |
| Increase (Decrease) in | | | | | | | |
| Prepaid expenses | 0.0 | 0.0 | -0.8 | 0.2 | -0.7 | 0.3 | 0.2 |
| Accounts Payable | 0.5 | -0.5 | 0.4 | 0.3 | 0.6 | -0.2 | -0.1 |
| Other | 0.9 | -1.1 | 0.7 | -0.8 | 0.0 | 0.0 | 0.0 |
| Net Cash (used in) | | | | | | | |
| Operating Activities | -4.1 | -10.7 | -17.7 | -27.2 | -45.3 | -40.3 | 64.8 |
| Cash Flow from Investment Activities | | | | | | | |
| Capital Expenditure | 0.0 | -0.2 | -0.8 | -0.2 | -0.2 | -0.2 | -0.2 |
| Other | -0.1 | -0.1 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Net cash provided by (used in) Investment activities | -0.1 | -0.2 | -0.8 | -0.2 | -0.2 | -0.2 | -0.2 |
| Cash Flows from Financings | | | | | | | |
| Common Stock & Exercise of Options | 0.0 | 15.6 | 0.1 | 0.0 | 0.0 | 0.0 | 0.0 |
| Notes Payable | 5.8 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Debt Financing Cost | -1.0 | 0.0 | -1.8 | 0.0 | 0.0 | 0.0 | 0.0 |
| Notes Payable issued under Reg D | 0.8 | 0.0 | 20.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Cash paid for deferred offering costs | -0.9 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Due to net increase/(decrease) in affiliates | 0.3 | -0.5 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Subscription receivable | 2.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Net Cash provided by Financings | 7.1 | 15.1 | 18.3 | 0.0 | 0.0 | 0.0 | 0.0 |
| Net Increase in cash and cash equivalents | 2.9 | 4.1 | -0.2 | -27.4 | -45.5 | -40.5 | 64.6 |
| Cash & Cash Equivalents, end of the year | 4.5 | 8.7 | 8.5 | -19.0 | -64.5 | -105.0 | -40.4 |

* Forecasts do not include planned fund raising

Source: Objective Capital

Appendix: Management

Dan Montano, Chairman & CEO, entrepreneur and co-founder of CardioVascular; former Board Member of Helen of Troy, Ltd, and former Investment Banker.

Dr Thomas Stegmann, Co-Founder and Chief Clinical Officer, Cardiac Surgeon, former Director of Thoracic and Cardiovascular Surgery at the Fulda Medical Centre in Germany. Pioneered the work on which CardioVascular was founded.

Dr John 'Jack' Jacobs, CSO and COO-Ex Hitachi Chemical, Merck and former Adjunct Professor at UCI School of Medicine. Also COO of Phage.

Mickael Flaa, CFO-Retired KPMG partner, CFO of Phage Corporation, CFO and Director of various companies.

Dr Kenneth Thomas, VP R&D-Retired Director of Growth Factor Research at Merck

Non-executive directors

Gary B. Abramovitz, Lead Independent Director, Chair of the Compensation, Audit, Corporate Governance, Conflict Resolution and Independent Director's Committees. Member of the European Compliance Committee. Deputy Chairman of Helen of Troy Ltd. Attorney and consultant to various law firms.

Wolfgang Priemer, PhD, co-founder, Chair of the European Compliance Committee. Private VC and executive in several European Companies from 1969-1999.

Joong Ki Baik, CEO of Seoul Angels Group Inc and CEO of Korea Bio-Development Corporation, a consulting and Asian bio-venture investment company. Executive Director of Economic Research Department, the Korean Chamber of Commerce and formerly with the Korea Exchange Bank.

Grant Gordon, Vice-Chairman, co-founder and President of Cardio-Phage International (CPI) and President of GHL Financial Services Ltd, an international financial services group.

Thomas Ingram, Independent Director- Private Investor, Former Broker/Dealer and Head of OTC trading/Office Manager for Troster Singer.

Robert Levin, Independent Director, retired since 1992. He previously owned Fredson RV which became Rogers Distributing, a major recreational vehicle sales and service company in Southern California.

Scientific Advisory Board

Ralph Bradshaw, Chairman, SAB-Professor, UCL. Renowned academic researcher into the structure and action of growth factors and protein turnover in eukaryotic cells.

John 'Jack' Jacobs, CSO, COO

Thomas Stegmann, CCO

Elizabeth Gordon, Regulatory Consultant ex Quintiles (CRO) and FDA

Kenneth Thomas, VP R&D.

CAD Phase II

(100 patients, 25 centers in 5 countries)

I. Entry

- 1-3 vessels disease based on angiographic stenosis
- Reversible cardiac ischemia
- CCS classification III or IV under optimal medical therapy
- Angina scores
- Angiographic documentation of atherosclerotic narrowing of a major coronary artery or diffuse type of CAD not amenable to bypass or angioplasty
- Stress and rest SPECTs
- Treadmill peak walking time (≥ 3 and ≤ 9 minutes)
- Quality of life questionnaires
- Exclusions include high cholesterol (>200), hypertension (systolic pressure >200 mm Hg), uncontrolled diabetes (Hemoglobin A1c $> 8\%$), which might jeopardize an angiogenic response

II. Treatment

- Proposed randomized to 40 high (20 $\mu\text{g}/\text{kg}$) and 40 low (0.6 $\mu\text{g}/\text{kg}$) dose FGF-1 treated patients plus an untreated 20 patient control group maintained on their optimal treatment (high and low dose FGF-1 group allocations are blinded).
- Mini-thoracotomy, minimally invasive robotic cardiac surgery and/or video-endoscopy guided surgery used to dose FGF-1
- 3 i.m. intramyocardial direct injections in up to 3 regions of stenoses

III. Follow-up (12 weeks after treatment)

- Proposed primary endpoint: SPECTs (summed stress score (SSS) per target segment) vs. baseline
- Proposed secondary endpoints:
 - Time to 1mm ST-segment depression by ECG
 - Exercise treadmill test duration, time to onset of angina and primary reason for stopping vs. baseline
 - Change in vascular bed density in treatment area as measured by angiography vs. baseline
 - Change in angina as measured by CCS Anginal Classification and Seattle Angina Questionnaire vs. baseline
- Safety and tolerability as measured by adverse events

PAD Phase Ia

(24 patients in 6 U.S. sites)

I. Entry

- Intermittent claudication for ≥ 6 months, stable for ≥ 3 months
- Resting ABI ≥ 0.4 and < 0.9
- Stenosis of $>70\%$ up to total occlusion in popliteal and/or tibial-peroneal trunk or at least 2 tibial arteries above the ankle; adequate inflow into the popliteal artery with $<50\%$ stenosis of the abdominal aorta, iliac, common and superficial femoral arteries as defined by either digital subtraction angiography (DSA), CT angiography (CTA) or Gd contrast-enhanced magnetic resonance angiography (CE-MRA)
- Gardner treadmill test peak walking times >1 minute and <12 minutes limited by pain in one or both calves
- Perfusion Gd CE-MRI spectroscopy of the calf muscles
- MR [^{31}P]phosphocreatine/phosphate calf spectroscopy
- Calf needle biopsy for muscle capillary density and capillary/muscle fiber ratio
- Quality of life questionnaire
- Exclusions include high cholesterol (>200), hypertension (systolic pressure >150 mm Hg), uncontrolled diabetes (Hemoglobin A1c $> 8\%$), which might jeopardize an angiogenic response

II. Treatment

- One set of bilateral i.m. injections (10/leg) adjacent to stenosis and into distal ischemic calf muscles
- Dosing groups: 8 patients per dose (6 treated with FGF-1 and 2 with the corresponding vehicle placebo control)
- FGF-1 dose levels: 3, 10 and 30 $\mu\text{g}/\text{kg}$
- Plasma PK will be measured over the first 24 hours.

III. Follow-up (week 12-13 visits)

- Primary endpoint: safety and tolerability
- Additional exploratory evaluations (vs. baseline):
 - Perfusion Gd CE-MRI spectroscopy of the calf muscles
 - MR [^{31}P]phosphocreatine/phosphate calf spectroscopy
 - Gardner treadmill test peak walking time
 - Angiography (DSA, CTA or Gd CE-MRA, same technique as used at baseline for each patient)
 - Calf needle biopsy for muscle capillary density and capillary/muscle fiber ratio
 - Quality of life questionnaires

Dermal Ulcer Healing Phase Ia

(8 patients in 2 U.S. sites)

I. Entry

- At least one, but no more than three, lower extremity full-thickness (extending through the dermis but not into the underlying muscle, tendon, cartilage or bone) diabetic or venous stasis ulcer
- Target ulcer of at least 8 week but no more than 1 year duration
- Limb with the target ulcer must have adequate blood flow as determined by transcutaneous oxygen pressure (TcPO₂) > 20 mm Hg at the dorsum of the foot and an ABI ≥ 0.4.
- Ulcer surface areas are measured by tracing and photography before and after debridement.
- Target ulcer area after debridement must be ≥ 1 cm² and the total of up to three ulcer areas ≤ 20 cm²; the largest ulcer is considered to be the target ulcer for evaluation.

II. Treatment

- Patients will be treated with topical FGF-1 and the ulcers then covered with a Bioclusive dressing. Venous ulcers will also be wrapped in standard compression dressings.
- 4 diabetic and 4 venous stasis ulcers will be treated with topical FGF-1. Half (2) of the patients with each type of ulcer will be treated with low dose (0.3 µg/cm²) and the other half (2) with a high dose (3.0 µg/cm²) FGF-1.
- Plasma PK will be measured over the first 24 hours post-dose.

III. Follow-up (day 7)

Primary endpoint: Safety and tolerability including:

- Signs of ulcer infection
- Ulcer surface area determined by tracings and photographs
- Any other adverse events

Alphabetical listing of commercial skin substitutes

| Product | FDA-Approved Indications (PMA, HDE, 510K, or other)* | Other Published Uses | Competitive Advantages | Disadvantages |
|--|---|---|---|---|
| Alloderm® <i>LifeCell Inc.</i> | Burns/full-thickness wounds (allograft) | Other formulations (Cymetra™, Repliform™) used to fill soft tissue defects in plastic, gyn, dental and urologic surgery | Not rejected; no cases of viral transmission after >100,000 product applications; 2 year shelf life | Lacks cellular components |
| Apligraf® <i>Organogenesis</i> | Venous/diabetic ulcers (PMA) | Epidermolysis bullosa; anecdotal reports, case studies and pilot trials in many other skin conditions | Mimics function of dermis; cryopreserved product | 5 day shelf life; awkward logistics of ordering and use |
| Biobrane® , Biobrane-L® <i>Bertek Pharmaceuticals</i> | Partial-thickness burns/meshed autografts/donor sites (510K) | | Three year shelf life; good barrier function and water exchange | No antimicrobial properties/temporary replacement requires removal in 7-10 days |
| Celaderm™ <i>Advance Biohealing Inc.</i> | (None) | Partial and full thickness burns, venous wounds | >6 month shelf life; relatively inexpensive; good results in many pilot studies | Not FDA approved |
| Dermagraft® <i>Advanced Biohealing Inc.</i> | Diabetic foot ulcers (PMA); ulcers secondary to epidermolysis bullosa (HDE) | | Mimics function of dermis; cryopreserved product | Difficult logistics of ordering and application; short shelf life (unless stored cryopreserved) |
| Epicel® <i>Genzyme Biosurgery</i> | Deep partial-thickness and full-thickness burns (HDE); congenital nevi (HDE) | | Autologous cells; no rejection, high incidence of permanent take | Fragile; custom preparation; one day shelf life; inferior cosmesis in many patients |
| EZ Derm™ <i>Brennan Medical Inc.</i> | Partial-thickness burns/venous, diabetic, pressure ulcers; porcine xenograft (510K) | | Relatively long shelf life | Potential immune response and/or disease transmission |

Appendix: Skin Substitutes

Alphabetical listing of commercial skin substitutes

| Product | FDA-Approved Indications (PMA, HDE, 510K, or other)* | Other Published Uses | Competitive Advantages | Disadvantages |
|--|---|--|--|--|
| Integra® <i>Integra LifeSciences</i> | Deep partial-thickness and full-thickness burns (PMA) | | Two layers; good barrier function; used in over 10,000 patients; moderate shelf life | Operative removal of silicone layer and autograft required |
| Laserskin® <i>Fidia Advanced Biopolymers</i> | (none) | Partial thickness burns, chronic venous, pressure ulcers, vitiligo | Autologous cells; no rejection; high incidence of permanent take | Two day shelf life; custom preparation; fragile |
| Oasis® <i>Healthpoint</i> | Partial/full-thickness pressure, venous and diabetic wounds/partial-thickness burns (510K) | | 1.5 year shelf life | Potential immune response |
| OrCel® <i>Ortec International</i> | Split-thickness donor sites (PMA); mitten hand deformity surgery of epidermolysis bullosa (HDE) | Venous and diabetic wounds | Mimics cytokine expression of healing skin; 9 month shelf life cryopreserved | Requires cryopreserved storage |
| TransCyte® <i>Smith & Nephew</i> | Full- and partial-thickness burns (PMA) | | 1.5 year shelf life frozen | Silicone membrane must be removed |

* PMA, pre-market approval; HDE, humanitarian device exemption; 510K substantial equivalence to predicate (previously approved) device

Source: David Eisenbud, MD, CWS; Ngan F. Huang, BS; Sunny Luke, DSc; Melvin Silberklang, PhD, Wounds 16(1):2-17, 2004

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Steven Zimmer, M. Sc. (Molecular Biology)
Steven has more than 25 years experience in analysis, corporate finance and as a portfolio manager in biotech and pharma including working for DLJ, CSFB and Robert Fleming in London, NY and Switzerland.

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