ISSN 1443-850X

Bioshares

Delivering independent investment research to investors on Australian biotech, pharma and healthcare companies

4 March 2016
Special Report: Tissue Therapies

Tissue Therapies Ltd (trading as Factor Therapeutics)

Key Financials
Share price: $0.044
Shares on issue: 302.578 M
Options on issue: 2.7 M
Market capitalisation: $13 M
12 month price range: $0.032 - $0.25

Board and Management
Dr Cherrell Hirst - Chair
Tim Hughes - NED
Dr Christian Behrenbruch - Executive Director

Bioshares is published by Blake Industry & Market Analysis Pty Ltd.

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Individual Subscriptions (48 issues/year)
$440 (Inc.GST)

This report has been commissioned by

TAYLOR COLLISON

Investment Report: Tissue Therapies Ltd (Trading as Factor Therapeutics)

The Preparation of this Report
The preparation of this report has been based on dialogue with company management, which provided corrections and clarifications through the drafting process as well as guidance on the market opportunity for VF-001.

Key Summary Points

- Tissue Therapies Ltd (trading as Factor Therapeutics) is developing VF-001, a recombinant protein, to treat chronic wounds such as venous leg ulcers.

- The development of VF-001 experienced a major setback in 2015 when the company failed to achieve European marketing clearance. The key reason the product was not approved in Europe was because the size of the safety database did not allow a reliable assessment of risk:benefit.

- Factor Therapeutics now intends to conduct a Phase II, randomised, controlled trial in the US. Although the focus is on the US market, the US trial has been designed with the consideration in mind that this data should also satisfy approval requirements for the European regulator including safety data requests.

- The company has refreshed the composition of its board and management in order to commercialise the company's lead product under a revised business plan.

- Following the Phase II study, Factor Therapeutics will consider licensing the program to a partner.

- The company is seeking to raise $15 million, principally to fund a Phase II trial. This financing, coupled to budget reallocations, if necessary, should be sufficient to complete the Phase II trial.

- In a 53 patient study of VF-001, some impressive results were achieved. These include: improvement of 77% of patients who had previously unhealed wounds for an average 33 months; 42% complete healing at 12 weeks in those patients who completed the study; complete healing in patients of wounds that had existed for 3.2 years, 5 years, 7 years and 11 years.

- The company has a solid intellectual property position with patent and protection out likely to at least 2030.

- Our assessment of the technology, competition and revised commercialisation program supports the development of VF-001 to address an unmet clinical need in the global venous leg ulcer market.

Terms

VF-001 *(Formerly branded as VitroGro) – current product*
Tissue Therapies *– Trading as Factor Therapeutics*
VLU *– Venous leg ulcer*
VitroCARD1001 *– European study with VF-001 in 53 patients*

Introduction

Factor Therapeutics is developing a recombinant protein, VF-001, for use in the treatment of wounds, specifically in venous leg ulcers, and also potentially using other formulations in wound care for the eyes following ocular surgery.

The therapy seeks to achieve attachment to the wound and skin cell migration and proliferation in the one protein that is delivered as a solution onto the wound.

Venous Leg Ulcers

Chronic leg wounds are a major clinical and healthcare challenge in the US, a key target market for VF-001. It is estimated that the prevalence in the US is 1% of the population, representing a serious unmet clinical need. Eighty per cent of leg ulcers have a venous component, where venous valves malfunction resulting in pooling of fluid in the lower legs contribute to over-saturation of the lower leg tissue. This can be due to varicose veins, obesity, age and smoking.

Venous leg ulcers can take weeks or months to heal, with recurring wounds very common. Wounds can last for years. The standard therapy is the application of multi-layer compression bandages that seeks to achieve a correct pressure differential between the veins and the arteries. After six months of standard treatment, 38% of wounds remain unhealed[1] and even for the most mild VLUs it takes up to six months of treatment to heal representing a massive healthcare cost.

The major feature of VF-001 as a VLU therapy is that it may improve healing times and ameliorate ulcer pain and thereby substantially reduce overall treatment costs. Patients who do not respond to multi-layer compression bandage therapy can be identified early on, after four weeks of initial treatment, however the company does not intend to restrict its product to this population.

1. Wound Repair and Regeneration (2014)22 688-693

Background

Tissue Therapies, trading as Factor Therapeutics, was registered as a company in 2002, to commercialise wound healing technology that was invented at Queensland University of Technology (QUT) following discoveries made in 2000. The company listed on the ASX in March 2004, raising $3.5 million.

Since listing, Factor Therapeutics has raised $56.9 million. Total contributed equity into the company at 31 December 2015 was $66 million, with the company having a cash balance at that time of $2.7 million.

The initial product Factor Therapeutics developed was a multi-protein complex of recombinant growth factors and extracellular matrix proteins that are naturally involved in skin biology (namely, IGF-1, IGF-binding proteins, epidermal growth factor and the extracellular matrix protein, vitronectin, which provides adhesion to the wound surface). These proteins have been shown to promote cell proliferation and migration in wounds.

The company completed several preclinical studies with this multi-protein complex and two clinical studies. The first clinical study was conducted in Perth (2008-2010) in 30 patients. The second clinical study was conducted in Canada (2008-2009) in 10 patients. Both trials achieved successful results in difficult-to-treat patient populations with a good safety profile.

2009

In 2009, Factor Therapeutics announced the successful preclinical testing of a new version of this therapy. Rather than mixing three separate proteins together, the company manufactured the one protein, called a recombinant mimetic protein, which had the critical domains of vitronectin and IGF-1. Why this is an improved version is because the new structure with the key vitronectin portion allows the IGF-1 growth factor to be quickly and fully bound to the wound bed.

In preclinical studies the new recombinant version, VF-001, achieved wound healing 12% faster than the original multi-protein complex. The new recombinant product was (and still is) manufactured by Eurogentec in Belgium, with the fill and finish packaging conducted by Catalent, also in Belgium.

2010

In 2010 the company conducted an open label study with VF-001 in Europe which recruited 53 patients. The trial was completed at the end of 2011. Results were highly successful with a very good safety profile.

November 2011 and March 2015

Between November 2011 and March 2015 (3.3 years) the company sought to gain regulatory approval in Europe but was unsuccessful due to an insufficient size of its safety data base and insufficient evidence of the utility of the IGF-1 component. During this time it conducted manufacturing scale-up of its product.

The company is commercialising the product as a ‘device with an ancillary medical action (IGF-1)’ in Europe, which is the classification awarded by the MHRA in Europe that has been accepted by the EMA.

2015

During 2015, management and board changes were effected, with the company’s Operations Director, Nigel Johnson, installed as CEO. The company is seeking to raise $15 million to fund further clinical development, with a focus to develop VF-001 for the US market as a biologic product.

Understanding What Went Wrong

An important consideration for potential investors in Factor Therapeutics is understanding the path that company has travelled along and where mistakes have been made and why.

Were the mistakes that have been made terminal for the business and the VF-001 program or does substantial commercial potential remain for VF-001?

If so, what is required to construct a profitable global product from this business?

Was it a process error (e.g. regulatory strategy) or was it a product error (e.g. a technical issue relating to product itself)?

How can future risks be ameliorated with a more disciplined and better structured business plan?

Reasonable progress 2004 – 2011

From listing in 2004 and the completion of its clinical studies at the end of 2011, Factor Therapeutics made reasonable progress in developing its wound healing technology.

Progress over this period included the completion of three clinical studies in three different countries – Australia, Canada and Europe – two with an earlier product based on the same wound healing biology and one with the current product. Results from these studies were consistently impressive, achieving excellent results in difficult-to-treat populations.

Over this period, the company also developed an improved version of its therapeutic product candidate, evolving it from a composition of multiple proteins (growth factors and vitronectin (the extracellular matrix)), to a recombinant single protein that incorporates the relevant binding domains of the previous product constituents (VF-001).

Benefits of improved VF-001

This was a significant achievement for the company. Not only did the new product improvement deliver a 12% increased rate of healing (in preclinical studies) using the same wound healing biology, but it delivered a number of other commercial benefits.

Benefits include reduced cost of manufacture and therefore potential higher margins, and a more consistent and definable product which will assist with regulatory clearance with respect to product consistency. Sourcing the manufacture of a single protein is also more straightforward than manufacturing several proteins.

European regulatory setback

The company's previous commercial strategy, which was a speed-to-market strategy, was to gain approval for its product first under a device classification in Europe. Upon approval in Europe, the company would have sought to raise additional funds and/or use cash flow from European sales to fund the more expensive clinical trials process in the US.

The company completed its European trial in September 2011. Its systems passed an audit at the end of October 2011 by an arm of the European regulator. In March 2015 the company was notified that it would need additional data (studies) before the product could gain European market clearance. No new clinical trials have been initiated since 2011.

There had been debate with the EMA about whether a device classification was appropriate by the MHRA which it has since been confirmed that it is.

The company has indicated that the major outstanding clinical item from the European

regulator is that it would like to see additional safety data, with a further 100 treated patients expected to be sufficient (i.e. "gives a 96% sensitivity for detecting adverse events occurring at a frequency of 3%") with the caveat that "chance safety findings may be clinically relevant and require more patients."

Had the company continued to conduct additional clinical studies to build a larger comparative database with the VF-001 while it was awaiting regulatory approval, it may well have had sufficient data now to meet the European regulator's data needs. However, a lack of funding dictated the company's strategy of using European sales to help fund further clinical development in other jurisdictions, namely the US.

Analysis

Between 2004, when the company listed, and November 2011, the company had a very productive period as previously described. However, a number of errors in respect of the company's strategy occurred, from the point of the company's AGM in October 2011.

No multi-centre, randomised, controlled clinical trial data

The first error was that since November 2011, additional clinical trials of VF-001 were not initiated, pending regulatory approval in Europe. The company believed it had sufficient data to gain approval from its 53 patient European study, making it 100% reliant on the outcome of this decision with no risk mitigation in place.

It is also surprising in light of views in a publication printed in 2011, from the inventors of the product and investigators involved in the first two studies of the first version of the product in Perth and Toronto. "While encouraging, randomised controlled trials are nevertheless required to determine the effect of the topical VN:GF complex treatment on the healing of chronic wounds compared with best clinical practices, and to determine which wounds will benefit most from treatment with the topical VN:GF complex." The company's approach now is to conduct a randomised, controlled clinical trial in the US, which we view as necessary and appropriate.

Change in marketing and distribution strategy

At the company's AGM in 2011, it announced a major change to its business model. Factor Therapeutics had always anticipated licensing the technology to a third party that would coordinate sales and marketing of the product. However in October 2011, the company announced that it would control sales of the product in Europe through a contract sales force from Quintiles, with distribution to be coordinated by Movianto.

In our view, this was a serious error by a company with access to funding subject to stockmarket conditions and sentiment towards the stock, that made the reliance on successful product approval in Europe even riskier. In our view, that approach failed, with commercialisation now having been stalled.

The company now plans to complete Phase II trial independently and to consider licensing the product to a third party at the completion of a randomised, controlled study in the US.

European Study with VF-001 [VitroCARD1001]

(July 2010 – November 2011)

The European study (VitroCARD1001) was the first and only clinical study with the version of the product that Factor Therapeutics is currently commercialising, VF-001.

The study was expected to start in July 2010. However, it was delayed by six months. Final data from the study was reported in November 2011, 16 months after the original expected start date, with a reasonably good recruitment rate once the trial was initiated.

Patient subset

The trial recruited 53 patients with hard-to-heal venous leg ulcers. Patients who had been receiving at least four weeks standard-of-care treatment prior to entering the study were enrolled into the study and then received weekly treatment of VF-001 for 12 weeks or until the ulcer had healed.

Patients' wound duration ranged from 2.0 months to 30 years. The average wound duration prior to entry was 33 months. The average age was 74 years with one patient being 100 years of age. A total of 45 patients completed the study. The remaining patients were part of the safety database but did not complete the treatment phase for reasons unrelated to the VF-001.

Treatment results

European study results were published in *International Wound Journal* in 2013. Our assessment of the results follows.

36% achieved complete healing

Complete healing was achieved in 19 of the 53 patients who entered the study (36%).

Contrary to expectations, healing success rates were not strongly proportional to lower wound duration rates. Of those patients who achieved 100% healing by around 12 weeks, four of the patients had existing wounds for more than three years, or specifically for 3.2 years, 5.0 years, 7.0 years and 11.0 years. A patient who was 100 years of age also achieved 100% complete healing.

The average wound reduction in the 53 patients was 46.7% at the completion of the study. However, considering only patients with wound duration of six months to five years, the average wound reduction per patient was almost identical at 46.6%.

The average wound reduction for patients with wounds only for longer than six months was 44%, and the average wound reduction in patients with wounds of duration of five years or more was an impressive 36% average reduction.

86% wound closure in 10.5 year wound

Another single impressive result was the 86% wound closure in a patient with a wound duration of 10.5 years, a 33.5% wound closure in a wound that had existing for 6.5 years and a 37.5% closure in a wound that had existed for 30 years.

Those patients who achieved 100% wound closure had an average wound duration prior to the trial of 22 months. This is lower than the overall population average wound duration (33 months), although that measure is skewed by two patients who had wounds for 30 years and 14 years. Removing these two patients would give an average wound duration in the 51 patients of 24 months.

77% of patients improved at 12 weeks

Overall, 41 patients (77%) of patients achieved an improvement in the wound size and 12 (23%) patients experienced a deterioration in their wound.

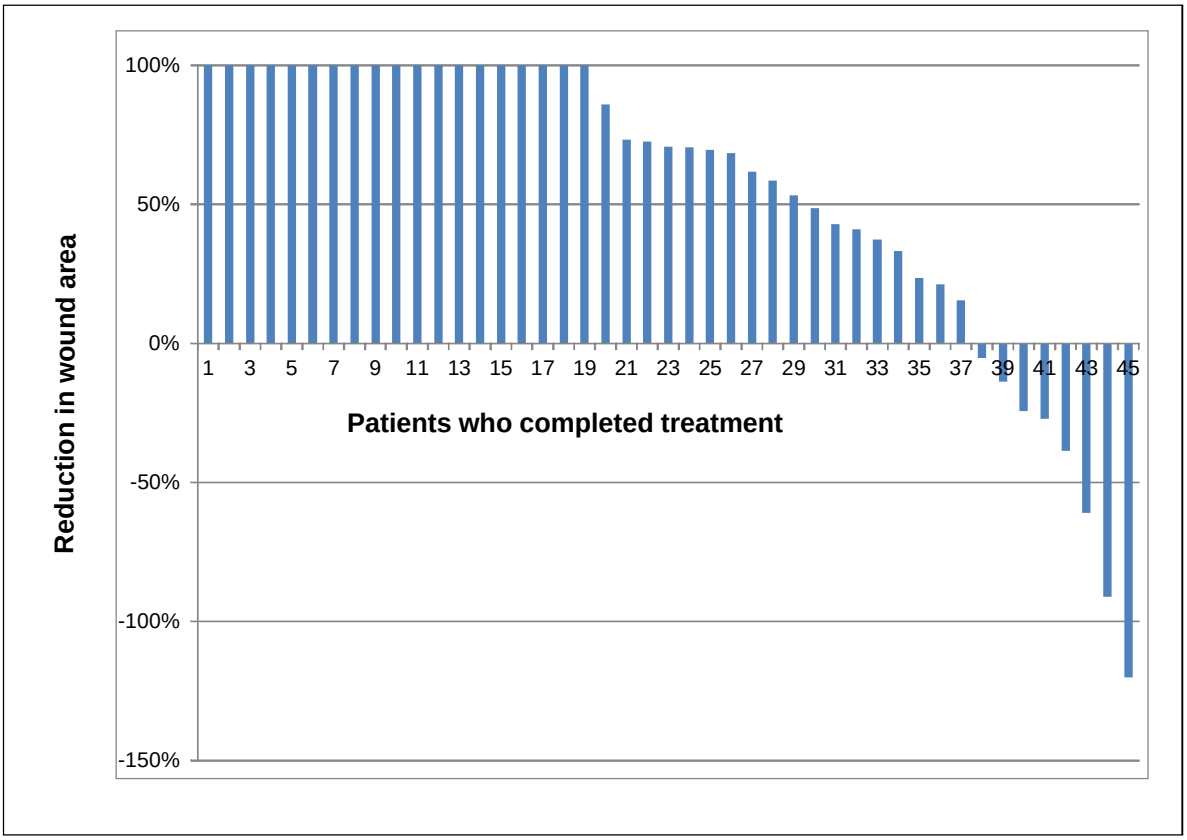
If patients who did not complete the trial are excluded, noting that no patients discontinued the trial due to the treatment, it is interesting to note that an average wound reduction per patient of 55% is achieved, with 42% achieving complete healing at around the end of the 12 week treatment using this measure.

With respect to pain, 11 patients reported an increase in their pain levels from baseline and 32 patients reported an improvement in pain levels.

Two serious adverse events occurred which were unrelated to the product. Of the 121 adverse events, there were none confirmed as being definitely or probably related to VF-001 treatment, although 20 events may have been possibly related but no plausible related events.

There were six cases of excessive tissue granulation, which may indicate rapid healing of the skin that could be attributed to VF-001. There were three cases of itching (pruritus), two cases of wound bleeding, and two cases of skin breakdown due to excessive moisture (maceration). None of these side effects appear overly concerning.

European Trial [VitroCARD1001] Results – Wound Closure Rates



Intellectual property – Patents

Factor Therapeutics has complete ownership of five patent families around the wound healing technology. These are listed in the table provided below.

The first patent family in the table relates to the earlier version of the product (protein complex). While it is not directly relevant to the current product, it would inhibit competitors following the company with a similar mixture (complex) of growth factors with vitronectin and delivers the company some broad claims in this area.

The second patent family, which is granted in the US and other regions, relates to the chimeric protein that includes the binding domain of the adhesion protein vitronectin. It is one of two core patents for the company and arguably the most important. It offers patent protection in the US out to between 2024-2026. There may also be the possibility of extending this patent protection in the US (and other US patents) through the patent extension process relating to the time involved in the regulatory approval process.

The third patent relates to a compound relating to fibronectin and IGF-1 for therapeutic use. It is not as strong as the previous patent. Only some of the claims in this original patent were granted in the US.

The fourth patent relates to second generation constructs. It has been granted in Australia, Hong Kong, Japan and Europe. It is under examination in the US. It was filed in June 2010, and gives patent protection in those regions granted to June 2031.

The fifth patent was filed in 2012 and is for potential application of the technology in the oncology field. It is pending in all regions.

Factor Therapeutics appears to have a solid patent position that will offer protection out to at least 2024.

There is extended protection available to VF-001 because it is a biologic, which confers four years data exclusivity. This status should extend protection out to at least 2030 and potentially beyond under current legislation.

Factor Therapeutic Patents Estate

	Name	Granted in US	US patent n.o.	Expiry in US	Other countries granted
1	Growth Factor Complex	Yes	7,514,398	2021	25 countries/regions
2	Growth Factor Complexes and Modulation of Cell Migration and Growth	Yes	7,659,367	2024-2026	22 countries/regions
3	Fibronectin: Growth Factor Chimeras	Yes	9,090,706	2030	Au & NZ, pending in three countries, under examination in four regions
4	Vitronectin: Keratinocyte Growth Factor Chimeras	No	-	-	Au, NZ & Japan (expiry 2031), pending in four countries, under examination in five regions including USA
5	Complex-Formation-Modulating Agents and Uses Therefor	No	-	-	Filed 2012 in Australia, Europe and USA

Current Commercial Strategy

In January 2016 the company articulated its revised strategy for commercialising VF-001. The company intends to raise $15 million in the first half of this calendar year in order to conduct a Phase II clinical study in the US in patients with venous leg ulcers.

The plan is to conduct the trial under an IND (investigational new drug) application with the product having been classified by the FDA's CBER arm as a biologic drug.

Randomised Controlled Study

That study will be a randomised controlled study, with approximately 100 patients receiving VF-001, and 100 in the control arm. Of those receiving VF-001, half will receive the same dose as used in the European trial and half will receive a higher dose. The company has made funding allowances for an extra 20% of patients in the study.

In the Phase II forthcoming study, all patients will be screened and treated with standard-of-care for four weeks. If they show improvement then they will be excluded from the study.

The aim of the trial is to gain more safety data around the therapy, as well as gaining efficacy data against the standard-of-care. While the emphasis is very much on commercialisation of the product in the largest healthcare market in the world, the US, the trial should also satisfy the data needs of the European regulator.

The company plans to have data from this study around September 2017 with which it can also satisfy the European regulator. It is expected that the trial will be run through a clinical network group in the US that specialises in wound care. There will be an interim readout of the data to assess trial progression.

It is expected that between 20-30 sites will be required with a six month enrolment period anticipated. A Principal Investigator for the study has been selected although details have not been made public. The trial is expected to start around July this year. At this point, it is expected that patients will be treated for 12 weeks with a 12 week follow-up period.

Factor Therapeutics submitted an IND in the US in mid 2013. This IND has been revised according to guidance from the FDA and an amended protocol is expected to be resubmitted to the regulator. The company has indicated that the FDA has no further manufacturing-related development requirements before commencing the forthcoming Phase II study.

The company still needs to manufacture finished product for the forthcoming Phase II US study. The finished product has a shelf life of at least three years. Previously manufactured finished product can not be used in this study. The company can use the bulk active material it has in stock, which will need to be formulated and packaged into a finished product.

The regulatory path for the US market has always been to have VF-001 assessed as a biologic not a device. In Europe, the company maintains its intention to have the product approved as a device where there is no explicit biologic classification according to the company.

Funding

The company has indicated it is seeking to raise $15 million by mid 2016. Of this amount, approximately $7 million is allocated for the US Phase II study. A further $3 million will be directed to product manufacture and $1.2 million for studying other indications for the product, such as ocular wound care after surgery, and potentially a filing of an IND for diabetic foot ulcers.

It is expected that the Phase II US clinical trial will be completed by September 2017. The funds to be raised will give the company 18 months clinical trial funding, and 24 months operational funding, out to March 2018.

The company expects to commence the Phase II trial within four months of completing the capital raising. Assuming the funding is completed it May, this sets the trial start date in September. For the trial to be completed by September 2017 indicates a 12 month duration.

Comments

Management has indicated that around February/March 2017 it will assess the trial progress. If this trial is slow to start or recruit, then the company can defer non-core spending to extend its financial runway by around 12 months.

The company is seeking to get an interim readout from the Phase II study, presumably once more than 60% of patients have been treated. This will give some early visibility on progress as well and will serve as a milestone for investors.

The company has factored in only $200,000 in annual R&D tax rebates based on historical spend and returns. The company may in fact be eligible for around $2.5 million in annual tax rebates. However, this will be a delayed payment and may be subject to policy changes by the Commonwealth Government.

The company has also taken into account a conservative foreign exchange rate (around AUD/USD of 0.65 against the US dollar).

The risk remains that initiation of the Phase II trial and recruitment could be delayed. While this remains a moderate risk, we believe the company could accommodate some *moderate* slippage in trial progress. Release of interim results may also provide the company with an upgraded revaluation event that may allow additional funds to be raised during the trial if required although it is not expected at this point.

Management

In April 2015, the company's long-standing CEO of 11 years resigned following the company's failed European registration strategy. The Operations Director, Nigel Johnson, was appointed CEO. In October 2015, Christian Behrenbruch, was appointed as an executive director, who currently works for the company officially two days per week.

Behrenbruch founded cancer antibody imaging company ImaginAb in 2007 in California and was CEO until 2015. While at ImaginAb, Behrenbruch raised seed funding, follow-on funding of US$33.5 million and non-dilutive funding of US$18 million. His expertise and interest in recombinant protein products is one of the reasons he joined Factor Therapeutics.

Behrenbruch is playing a leading role in re-commissioning and re-designing the commercial development of VF-001 and is well placed to guide the company in that role. He has a two year contract with an option to extend the contract for an additional year at the board's discretion.

A number of board changes occurred also in 2015. Chairman Roger Clarke (also chairman of Morgans Corporate, which raised most of funds for Factor Therapeutics) resigned last year, as did Mel Bridges and Iain Ross. Dr Cherrell Hirst joined the board last year as chairman, and Dr Christian Behrenbruch also joined the board as an executive director. The third and existing board member is Tim Hughes.

We understand further additions to the board are planned over the medium term.

The company has established a US subsidiary which is expected to employ two staff to assist with managing and monitoring the US clinical study.

QUT Arrangement

The original VF-001 technology was discovered at the Queensland University of Technology (QUT). At 30 June 2015 QUT had a 2.6% stake in Tissue Therapies (Factor Therapeutics).

Previously, the intellectual property rights to the inventions relating to this technology had been assigned to Factor Therapeutics whereby QUT received a shareholding in the company, Factor Therapeutics was required to conduct research activity for at least $300,000, and pay 4% of any revenue it received to QUT from the sale of any product or service developed from the licensed patents, in countries where patents issue.

In July 2015, the five patent families around the VF-001 technology were transferred to Factor Therapeutics and a new research agreement was formed QUT which has significantly lower financial obligations by Factor Therapeutics to QUT.

Health Economics Analysis – Early Work

Factor Therapeutics had previously engaged consulting group, Global Health Economic Projects, to conduct a health economics assessment of using VF-001 with standard care in comparison to existing standard care.

That report factored in a pricing of VF-001 in the UK of between £30 – £50 per treatment, applied weekly for up to 12 weeks, which included different pricing for treatments in community care settings or specialty care. An analysis was also conducted to assess the potential healthcare savings in Germany, based on a price of € 30 – € 50 Euros per week for up to 12 weeks treatment.

The report found that a health cost saving of 11% could be achieved in Germany and a 15% saving in treatment costs in the UK if VF-001 treatment was used rather than the existing standard care alone.

This research needs to be revised and updated due to the expansion of the clinical database.

Addressable Market for VF-001

Venous leg ulcers

The prevalence of venous leg ulcers in the US is estimated at 1% of the population. While the exact market size is difficult to estimate, it represents a multi billion dollar addressable market worldwide.

The market for venous leg ulcers with existing products and treatments remains poorly served, with 38% of wounds remaining unhealed after six months of standard treatment. Even the mildest VLUs take up to six months treatment with existing graded compression bandage therapy to achieve healing. Accelerating this healing process in the community setting offers considerable savings to healthcare costs.

While advanced wound care products such as placental-derived skin substitutes have found a place in treating smaller diabetic ulcers, there remains a strong need for improved and reliable treatments for venous leg ulcers particularly at the community care level.

Competitive Landscape

The current standard-of-care for the treatment of venous leg ulcers involves graded compression bandage therapy. According to the company, the vast majority of VLUs are treated in the community setting by nursing staff and this is the area where Factor Therapeutics will be positioning its product VF-001.

Increasing the rate of healing of VLUs represents a multi billion dollar market worldwide. Currently skin replacement products, such as Epifix from MiMedx, are emerging as an effective treatment for diabetic foot ulcers. However, this is a crowded therapeutic area. In general these therapies are considerably more expensive than the VF-001 product, which has a lower cost-of-goods and a lower cost of administration (via nursing staff versus specialist care).

The treatment of VLUs is an area of unmet medical area in need of new approaches that can improve the rate and level of healing in chronic wounds.

In analysis conducted comparing the results of VF-001 from the 53 patient European study with a matched data base of patients with VLUs from the UK and Germany, it was found that over a forecast 90 day healing process, VF-001 with standard-of-care treatment accelerated healing by a median 9-14 days over standard-of-care treatment alone.

An analysis by Global Health Economics Projects, which forecast longer term healing over a 365 day period, was calculated as improving time to healing by between 103 – 248 days when VF-001 was compared against matched UK databases of VLUs. It should be noted that this analysis conducted by others was a retrospective analysis only. The company will generate prospective data from its forthcoming randomised controlled study.

Key Investment Risks for Therapeutic Product Developers

The company and its securities, as described and discussed in this report, are subject to the following key risks. The risks are described in general terms, but are highlighted as key risks. These key risks are therefore not inclusive of every risk pertaining to this company and its securities.

Clinical Trial Risks

A set of risks with companies developing therapeutics products is that clinical trials may run over budget and past their planned completion dates because of delays in gaining ethics approvals, in signing on clinical trial sites, in achieving an expected rate of recruitment because of competition for patients, and sometimes because the complexity of the therapeutic product being evaluated in the clinic reveals new insights into other factors.

Clinical trial design may not cause a trial to run over time. However, the risk that a design may yield a statistically insignificant result should be considered. A trial design may have included an endpoint that is not meaningful in terms current clinical practice. A trial design may have been underpowered i.e. had not been designed in terms of the number of patients to be screened, recruited and finally evaluated to deliver a recognisably statistically valid result.

Personnel Risks

Therapeutic product development companies depend on skilled, specialist personnel to achieve their business objections. Loss of skilled, specialist personnel can contribute to setbacks and delays with development programs if mitigation plans have not been put in place.

Partnering Risk

Companies that partner (license) therapeutics products for further development and marketing by a larger company are subject to the risk that the licensee will discontinue the development of the asset, for both commercial and non-commercial reasons.

Obsolescence

A risk exists that a therapeutic product becomes obsolescent while it is in development, because of the emergence of new scientific and clinical data, or the introduction of new standards of care.

Regulatory

Therapeutic product development companies are regulated by organisations such the USA's Food and Drug Administration, the European Medicines Agency (EMA), Japan's Pharmaceuticals and Medical Devices Agency, the China Food and Drug Administration (CFDA) and Australia’s Therapeutic Goods Administration.

The rules and regulations that govern these bodies and the rules and regulations they enforce are paramount, covering both therapeutic product development and marketing.

A risk that therapeutic product companies face at the regulatory level include failure to achieve necessary consents, including marketing authorisations, because of inadequate submissions for clinical development programs and for product approval. A failure to understand and follow agency guidance is another source of risk

Technology

A fundamental risk is that the embodiment of a company's invention in a therapeutic product is found, through a process of rigorous clinical evaluation, to not be safe, or to be safe but not efficacious, or to be found neither safe nor efficacious.

Manufacturing

In terms of manufacturing, therapeutic products can run the risk of being too expensive to make, with scale-up of manufacturing capable of addressing an appropriate cost of goods a key development threshold.

Key Investment Risks (cont'd)

The manufacture of, and testing of therapeutic products for consistency and purity (where relevant) may fail to meet expectations and therefore may have to be repeated, following changes to manufacturing methods or to analytical methods.

Freedom to Operate (IP)
Patents confer to the proprietors of a granted patent a period for exclusive exploitation of an invention. However, a company may run the risk that where a therapeutic product relies on multiple inventions, it may be found to have infringed one or several patents. Therefore, unexpected costs may be incurred in securing access to the relevant intellectual property, or such costs are prohibitive and force the abandonment of a product's commercialisation.

Pricing and Competition
The presence of new and emerging competitor products is a risk for therapeutic product developers. Similarly, competitor product pricing, coupled to 'whole of treatment' costs, is a source of risk for therapeutic product developers.

How Bioshares Rates Stocks

For the purpose of valuation, Bioshares divides biotech stocks into two categories. The first group are stocks with existing positive cash flows or close to producing positive cash flows. The second group are stocks without near term positive cash flows, history of losses, or at early stages of commercialisation. In this second group, which are essentially speculative propositions, Bioshares grades them according to relative risk within that group, to better reflect the very large spread of risk within those stocks. For both groups, the rating "Take Profits" means that investors may re-weight their holding by selling between 25%-75% of a stock.

Group A

Stocks with existing positive cash flows or close to producing positive cash flows.

Buy	CMP is 20% < Fair Value
Accumulate	CMP is 10% < Fair Value
Hold	Value = CMP
Lighten	CMP is 10% > Fair Value
Sell	CMP is 20% > Fair Value

(CMP–Current Market Price)

Group B

Stocks without near term positive cash flows, history of losses, or at early stages commercialisation.

Speculative Buy – Class A

These stocks will have more than one technology, product or investment in development, with perhaps those same technologies offering multiple opportunities. These features, coupled to the presence of alliances, partnerships and scientific advisory boards, indicate the stock is relative less risky than other biotech stocks.

Speculative Buy – Class B

These stocks may have more than one product or opportunity, and may even be close to market. However, they are likely to be lacking in several key areas. For example, their cash position is weak, or management or board may need strengthening.

Speculative Buy – Class C

These stocks generally have one product in development and lack many external validation features.

Speculative Hold – Class A or B or C

Sell

Corporate Subscribers: Cogstate, Bionomics, Impedimed, LBT Innovations, Viralytics, Phylogica, pSivida, Benitec BioPharma, Invion, Imugene, Analytica, Circadian Technologies, Reproductive Health Science, Regeneus, Innate Immunotherapeutics, Anatara Life Sciences, ResApp, Pharmaxis, Starpharma, Antisense Therapeutics, Atcor Medical

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