

# VIRAX HOLDINGS (VHL)

## Clinical Trials set to begin on Promising Skin Cancer Immunotherapy

### SPECULATIVE

29 April 2011

#### Share Trading Info

ASX Code	VHL
Current Share Price (per share)	2.6c
Trading Low /High (Rolling Year)	2.5c - 9.1c
Market Capitalisation \$m	4.7

#### Issued Capital (m)

Ordinary Shares	180.7
Conv Notes (redeemable @ 14c)*	7.9
Unlisted Options	6.8
<b>Total Diluted Shares</b>	<b>203.3</b>

\* conv into 2 ordinary shares

#### Board of Directors

Michael Humphris	Non Executive Chairman
Ian Pyman	Non Executive Director
Tim Cooper	Non Executive Director

#### Executive Management

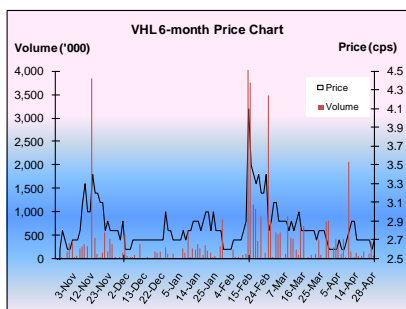
Dr Larry Ward	Chief Executive Officer
John Morrison	CFO & Company Secretary

#### Major Shareholders

Tim Cooper	6.2%
Dr Keong Lim	5.9%

#### Important Disclosure

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### SUMMARY

**VHL have entered into a License Agreement with French-based Transgene to further develop Transgene's TG1042 product. TG1042 is a clinical stage skin cancer immunotherapy which has previously shown promising anti-tumor activity and clinical benefit in cutaneous lymphoma, a rare form of skin cancer.**

**VHL is planning to move quickly into Phase I/IIa clinical trials this year in the very large Basal Cell Carcinoma (BCC) market. This rapid development is possible because of the previous clinical testing of TG1042 by Transgene in cutaneous lymphoma. BCC is the most common form of skin cancer. The most common type of BCC is nodular BCC (nBCC), accounting for up to 70% of BCC diagnoses.**

**The company will specifically target nBCC in its trials, with a view to positioning TG1042 as an attractive alternative to surgery (currently the primary treatment for BCC and nBCC), for both the surgeon and the patient, as there are numerous complications associated with surgical treatment of nBCC on the face, head and neck.**

**The licensing agreement builds on the existing relationship of VHL with Transgene, whereby Transgene are currently utilising VHL's Co-X-Gene™ technology to develop two products with cancer applications – TG4001 and TG4010. Under the licensing agreement, VHL is to receive milestone payments and royalty on the net sales of these products.**

#### Attractive market potential

Research undertaken by VHL has estimated a market potential in 2018 of up to US\$500 million peak sales based upon a future price per treatment for TG1042 in the range of A\$750-1000, varying by market and a pool of up to two million patients worldwide with nBCC.

#### Market Positioning - An alternative to surgery

The pool of nBCC patients is very large and there is an unmet medical need for new, non-surgical treatments for patients with nBCC for whom surgery is not an ideal therapeutic solution.

Intralesional treatment with TG1042 may be an attractive alternative for both the surgeon and patient for such difficult surgeries. It could be used either as a replacement for surgery or in conjunction with surgery. That is, the lesion clears or is reduced in size by treating with TG1042 before surgical excision thus allowing the surgeon to employ an adequate surgical margin to minimise recurrence.

Further, prior human testing of TG1042 in other skin cancer applications has lowered the technical risk of the project in nBCC.

### **Clinical trials in Australia planned; target mid 2011 commencement**

VHL is currently in discussions with the Therapeutic Goods Administration (TGA) in order to obtain regulatory approval to commence clinical trials in Australia by mid 2011. Should clinical trials commence in mid 2011, VHL expect results from the first clinical trials in the first half of calendar 2012. The aim of the upcoming trials is to prove that TG1042 is safe, well tolerated and has clinical effect in patients with primary nBCC. Transgene have conducted Phase I and Phase II trials for TG1042 and found that the product worked in other skin cancer applications.

One strength of the proposed trial is that it will have major efficacy endpoints as well as safety and tolerability. The efficacy endpoints are Clinical response (effect on lesion size) and histological response (the lesion will be examined for clearance of cancer cells).

### **Transgene to assist VHL with clinical trials**

Transgene are providing VHL considerable support to move to clinical testing within months. This includes an extensive data package of manufacturing and testing procedures, non-clinical testing results in animals as well as data of prior human clinical trials. Also, importantly, enough fully manufactured and tested material is to be provided for Phase I and II trials. Hence, VHL are effectively avoiding the long lag time (4-5 years) typically required for the product to be manufactured, tested and shown to be safe for human clinical testing. The company expects the product to be available on the market in 5-7 years.

### **Regulatory Risks Reduced**

The prior successful track record of obtaining approval for clinical testing of TG1042 by regulators from major world pharmaceutical markets such as the US, Switzerland, France and Germany has effectively reduced the regulatory risk in relation to future regulatory approvals. Regulatory authorities in these jurisdictions have reviewed manufacturing, pre-clinical packages as well as the prior human clinical trial packages.

### **Capital raising planned to fund clinical trials in Australia**

VHL is proposing to raise approximately \$2.5 million to fund clinical trials in Australia, ongoing corporate costs and general working capital. Given industry standards and the high costs of human clinical trials, the VHL proposed trials are inexpensive.

The core trial cost is expected to be between \$0.8 million to \$1.5 million. Should additional funding become available (i.e. beyond the amount sought), VHL may increase the patient trial numbers to further enhance the output of the trials. The trial design is currently being finalised. In broad terms, the initial trial will target from 20-40 patients with a primary nBCC (non-metastatic disease) and will be further refined after discussions with the TGA.

### **VHL to utilise TG1042 produced in Transgene's manufacturing facility for Phase I and Phase II testing**

The manufacture of TG1042 clinical batches was undertaken at Transgene's 2,500m<sup>2</sup> multi-purpose manufacturing facility in France. This material will support Phase I and II clinical studies. VHL are currently in discussions with potential contract

manufacturers to produce TG1042 in larger quantities for future large scale Phase III clinical trials and eventual commercial scale production.

## **1. Background and Terms of Agreement for TG1042**

In February 2011, VHL announced that it had signed an exclusive license agreement with Transgene for VHL to develop Transgene's TG1042 product (Adenovirus-interferon-gamma, or Ad IFN- $\gamma$ ), which is a skin cancer immunotherapy.

*License Agreement on TG1042 favourable for VHL*

Under the agreement, Transgene will assist VHL with technology transfer in order to facilitate further clinical trials as well as provide an appropriate amount of clinical grade TG1042 for the clinical trials planned in Australia. The agreement also gives VHL worldwide rights to TG1042.

Further, there are no upfront payments to Transgene required by VHL on executing the license. The principle commercial terms of the license agreement for TG1042 (under which VHL has acquired rights to TG1042) include a global license, the right to a sub-license, a milestone payment to Transgene on first product approval, a royalty payable to Transgene on sales of TG1042 by VHL and a portion of VHL net receipts from sub-licensing to be paid to Transgene.

*VHL has demonstrated to Transgene an ability to conduct further trials in a larger market*

Transgene have put considerable resources into TG1042 over a number of years and have supplied VHL with a substantial data package. In addition, Transgene have developed a commercially scalable manufacturing process, with all of the associated testing.

Transgene did not progress the product further - not for technical reasons as the TG1042 met all its milestones in the clinical trials - but for commercial reasons, as cutaneous lymphoma is a rare disease and was not considered a viable commercial target for Transgene to continue further development<sup>1</sup>. Instead, Transgene were looking to enter into a deal where the product can be used in a larger market, such as BCC, and where a partner (i.e. VHL) is able conduct clinical trials in Australia, where BCC is a major problem.

## **2. What is TG1042?**

Transgene's skin cancer program is based on an antigen-independent immunotherapy platform. Transgene has developed a gene transfer approach, which is based on a replication deficient adenovirus type 5 (Ad5) carrying the human IFN- $\gamma$ .

TG1042 which is designed for direct intra-tumoral injection is a harmless virus that produces the cytokine, interferon-gamma (IFN- $\gamma$ ), which has well known direct anti-cancer properties as well as an ability to modulate the immune system to target cancer cells. Recombinant protein forms of IFNs have previously been used with good effect for the treatment of BCC. However, their widespread use has been discontinued as multiple injections by the doctor into the tumour (up to 9 times over a three week period) is required. This was not practical from both a patient and doctor perspective. TG1042 circumvents this problem as expression of IFN- $\gamma$  by the virus lasts 1-2 weeks.

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<sup>1</sup> To illustrate, there are approximately 55 cases of cutaneous lymphoma reported per year in Victoria compared to 27,000 cases of BCC.

TG1042 exerts its effect by inducing a dual interferon response with type 1 (IFN- $\alpha$ ) and type 2 (IFN- $\gamma$ ) interferons, the type 1 expression being induced in the tumor cells when the adenovirus infects them and the type 2 interferon being produced directly by the TG1042.

### **3. Results from Transgene Clinical Trials**

Transgene have tested TG1042 extensively in pre-clinical safety and efficacy models and on the basis of this, Transgene have been able to complete Phase I and Phase II clinical trials in human skin cancer indications for the treatment of cutaneous lymphomas. Clinical data from Phase I and Phase II trials with TG1042 suggests that the local administration of adenovirus IFN- $\gamma$  is safe and demonstrates anti-tumor activity with clinical benefits. This treatment was highly promising and on this basis was awarded Orphan Drug status by the European medical regulatory body, European Medicines Agency (EMA) for the treatment of Cutaneous T cell Lymphomas.

Phase I/II trials were performed in a total of 39 recruited patients with either advanced primary cutaneous T-cell lymphoma (CTCL) or multilesional cutaneous B-cell lymphoma (CBCL), which is a rare form of skin cancer. The treatment induced a high overall response rate of local clinical responses: 54% of 33 evaluable patients responded to the treatment. All five patients with CBCL responded to the TG1042 treatment (100% response rate). The duration of response in some CBCL patients was long-lasting (>1 year).

Given the encouraging responses in patients with CBCL and the absence of therapeutic alternatives to radiotherapy for these patients TG1042 was further developed for CBCL. In Phase II studies in patients with relapsing primary cutaneous lymphomas, the primary endpoint was met in the first step of the Phase II trial as measured by an overall objective response rate of 83%.

Adverse events from the trials were minimal, with the most commonly observed adverse events being injection site reactions, flu-like symptoms and fatigue. In addition, there were no seriously adverse events.

### **4. Overview of the Global Skin Cancer Challenge**

Skin cancer is the most common form of cancer worldwide, accounting for one in three cancer diagnoses each year. Skin cancer is found in most developed countries, often at alarmingly high incidences:

- There are currently 2-3 million skin cancers occurring annually worldwide (according to Skin Cancer Foundation)
- One in every five Americans will develop skin cancer during their lifetime (according to Skin Cancer Foundation)
- Incidence of skin cancer in North America, Europe and Australia is increasing 3-6% annually.

The most common form of skin cancer is BCC. According to a survey of skin cancer<sup>2</sup>, non-melanoma skin cancers such as BCC and squamous cell carcinoma alone accounted for nearly 90% of all skin cancer diagnoses. BCC accounts for an estimated 75% of non-melanoma skin cancers, with nBCC being the most common form. Most nBCC lesions

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<sup>2</sup> Garner, KL and Rodney, WM. Basal and squamous cell carcinomas. Primary Care. 2000; 27(2):157-163

occur in the face, neck and head, which complicate the process of surgical excision.

Though non-melanoma skin cancers are generally benign and account for only an estimated 1,000-2,000 deaths per year, in the aggregate skin cancers do constitute a major healthcare challenge. Treating dermatologists consider BCC as a chronic disease with two-thirds of patients treated for primary BCC lesions developing new lesions elsewhere on the body within five years following initial treatment and a further 18% recurring between years 5-10 post-treatment. Recurrence and re-treatment adds to the ongoing healthcare cost for this patient pool.

A variety of treatment modalities have been developed for BCCs including electrodesiccation, curettage, cryosurgery, radiation, topical imiquimod and 5-fluorouracil. While these treatment modalities are suitable for some histological subtypes of BCC such as superficial BCC (sBCC) they are not effective for nBCC, for which surgical excision remains the gold standard.

Primary treatment for nBCC is surgical excision. The cure rate for surgical excision ranges from 90-98% as reported by the American Cancer Society. Five year clearance rates are somewhat lower, in the 90-95% range<sup>3</sup>. It is estimated that for surgical excision of nBCCs, about one quarter can be classified as difficult surgeries, due to their size or anatomical location (e.g. close to eyelids) or that the surgery is potentially cosmetically disfiguring. Successful surgical treatment requires leaving a clean margin, histologically clear of cancer cells and, for a significant number of patients with nBCC in the face and head, this is problematic and can lead to higher relapse rates.

Intralesional treatment with TG1042 may be an attractive alternative for both the surgeon and patient for the difficult surgeries described above.

**Table 1: Market Positioning of TG1042**

<b>Medical Need/Unmet medical needs</b>	<ul style="list-style-type: none"> <li>• Cosmetic (avoid scarring)</li> <li>• Therapy when surgery is considered inappropriate (e.g. for difficult to perform surgeries (approx. 25%) or patient possessing contraindications)</li> <li>• QoL issue - not life threatening</li> </ul>
<b>Value Proposition</b>	<ul style="list-style-type: none"> <li>• Safe &amp; effective treatment alternative when surgery is inappropriate</li> <li>• Complementary (neo-adjuvant) to difficult surgeries</li> <li>• Treatment of relapsers (5%-10%)</li> <li>• Potential positioning towards wider Dermatologist community</li> </ul>
<b>Current competition &amp; Gold standard</b>	<ul style="list-style-type: none"> <li>• Histology controlled surgery (excision)</li> <li>• Very high efficacy for Surgery (~90%), this efficacy ratio is a clear benchmark</li> </ul>
<b>Clinical advantage vs Gold standard</b>	<ul style="list-style-type: none"> <li>• Better Quality of Life (lower risk of scarring, less invasive)</li> <li>• Potentially better cost effectiveness (for cases leading to hospital stays)</li> </ul>
<b>Physicians/Patients target</b>	<ul style="list-style-type: none"> <li>• <b>Patients:</b> 1st line therapy alternative to difficult surgery</li> <li>• <b>Physicians:</b> Surgeons &amp; Dermato-Oncologists; Wider dermatological community (second step)</li> </ul>

Source: VHL Presentation, 10 March 2011

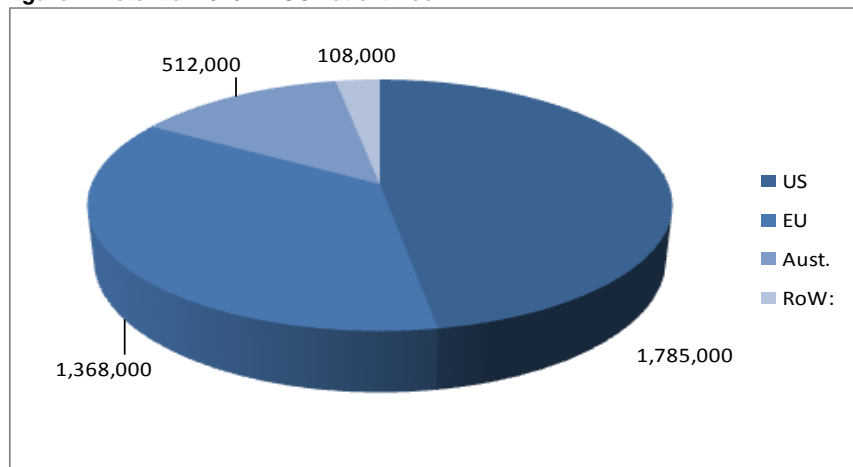
<sup>3</sup> Silverman et al. Recurrence rates of treated basal cell carcinomas, Chapter 3, Surgical Excision. J Dermatol Surg Oncol. 1992; 18:471-476

## 5. Market Opportunity for TG1042

Research undertaken by VHL has estimated a market potential in 2018 of up to US\$500 million peak sales based upon a future price per treatment for TG1042 in the range of A\$750-1000, varying by market and a pool of up to two million patients worldwide with nBCC.

A recent study of the global dermatology market by the market research firm Frost & Sullivan (F&S) estimated the global incidence of non-melanoma skin cancer (NMSC) in 2008 at 2.75 million increasing to 3.48 million in 2016. VHL currently project market introduction of TG1042 to treat nBCC in 2018 and assuming an overall incidence growth rate of NMSC of 4% per year and applying this rate to the F&S projections for 2016, results in a potential 2018 NMSC patient pool of 3.733 million. The breakdown of this is shown below.

**Figure 1: Potential 2018 NMSC Patient Pool**



**Source: VHL**

BCC accounts for most of the NMSC diagnoses worldwide. Estimates for the US indicate that BCC accounts for about 75% of all skin cancer diagnoses. Applying this calculation to the worldwide skin cancer figures projected by F&S indicates a total BCC patient pool of 2.75 million in 2018. The British Journal of Dermatology estimates that nBCC accounts for 62-70% of all BCC diagnoses. Using these assumptions results in a projected pool of nBCC in 2018 that ranges from 1.705 million to 1.925 million. This is the target population for the initial indication for TG1042.

Based on estimates of current therapeutic costs and projected future clinical development expenses, VHL are projecting a future price per treatment for TG1042 in the range of A\$750-1000, varying by market.

Australia is typically regarded as a small market for pharmaceuticals by world standards. However the size of the skin cancer problem in Australia makes it an appreciable market in its own right. The attractiveness of the Australian market for TG1042 is underpinned by the following factors<sup>4</sup>:

- Two in three Australians will be diagnosed with skin cancer in their lifetime.
- Australia has one of the highest incidence of skin cancer in the world, nearly four times the incidence in the US and Western Europe.
- Skin cancer is the most expensive cancer in Australia and the 5<sup>th</sup> most expensive cancer in the US.

## **6. Manufacturing Process**

A commercially scalable manufacturing process with associated testing performed according to clinical Good Manufacturing Practice (cGMP) has been developed for TG1042.

Manufacture of TG1042 of the clinical batches to be used in the Phase I and II trials was undertaken at Transgene's 2,500m<sup>2</sup> multi-purpose manufacturing facility, located in Illkirch, France (approximately 400 kilometres east of Paris).

The manufacturing process covers the entire process (production, purification, filling and storage) and meets cGMP guidelines for the environmental and quality control.

VHL has commenced discussions with an appropriate and recommended manufacturer capable of handling late-stage clinical development and commercialisation.

TG1042 is produced as a viral suspension and is formulated in sterile fill glass ampoules for injection. Finish filled ampoules are stored at -70°C with stability trials ongoing.

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<sup>4</sup> According the Cancer Council of Australia

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