QBiotics Group

SHAREHOLDER UPDATE

August 2023

KEY POINTS / HIGHLIGHTS

- Overall, there has been good progress in our human oncology trials of tigilanol tiglate with recruitment rates picking up and positive read-outs of results from earlier trials.
- Since June, three patients have been treated in our Phase II clinical trial in soft tissue sarcoma (STS) and one additional patient (total of three) in our head and neck cancer (H&NC) trial; a further three patients (2 for STS, 1 for H&NC) have consented and are awaiting treatment.
- An application to the US Food and Drug Administration (FDA) for orphan drug designation (ODD) for tigilanol tiglate for treatment of STS is in preparation.
- A new clinical trial site in Brisbane opened to boost patient recruitment in QB46C-H08 H&NC trial and plans have advanced for a further site to open at a major clinical centre in France.
- Safety and efficacy endpoints have been met in our Australia-India head and neck squamous cell carcinoma dose escalation trial with tigilanol tiglate (QB46C-H03). Exploratory data from assessment of tumour biopsy samples in this study provided further evidence of tigilanol tiglate's mode of action in inducing an immune response against tumour tissue in humans.
- Formal results from the three patients recruited in the melanoma combination study (QB46C-H06) indicated that low dose tigilanol tiglate in combination with pembrolizumab (Keytruda®) was safe and tolerated, with one patient achieving Complete Response of the treated tumours and no local recurrence at 15 months. In this patient a non-injected tumour at a distal site also responded.
- Tigilanol tiglate commercialisation activities have progressed with:
  - Appointment of a Chief Medical Officer and a Business Development advisor with experience in biotech and oncology partnering to further strengthen the company's clinical and product partnering teams;
  - QBiotics presence and presentations at major international pharmaceutical partnering and drug development conferences;
  - Invitations to specialist healthcare meetings; and,
  - Initial discussions with target partner companies.
- A review of the marketing strategy for STELFONTA® is underway with Virbac.
- Veterinary clinical trials to inform human 'pan-tumour' application of tigilanol tiglate are in recruitment or in reporting phase.
- The Protocol for the first-in-human Phase I/II safety trial of our wound healing drug EBC-1013 in patients with venous leg ulcers is under final review prior to submission to regulators.

- A key patent on use of tigilanol tiglate in combination with immune checkpoint inhibitors has been granted in Europe and this now completes our coverage for this invention in all major international jurisdictions.
- New patent applications on (i) use of tigilanol tiglate monotherapy to induce effects in distal untreated tumours and (ii) disruption of microbial biofilms by EBC-1013, have entered National Examination phase in key jurisdictions.
- An independent review of the full Board is being initiated to identify future skill requirements for the next stages of the company's growth and development.
- Measures to conserve cash are being implemented through all areas in the company including reducing internal costs for STELFONTA® activities, reducing travel costs, no salary increases awarded to staff or Directors, and the CEO waiving her right to any personal bonus awards.
- Cash at bank as of 30 June 2023 stands at AU$59.1M. Cash burn for Q4 FY2023 was $5.3M, which compared well to the previous quarter (Q3 cash burn of $7.8 M).

Dear Shareholders,

I am pleased to provide the following shareholder update on progress of activities within QBiotics Group Limited (QBiotics).

Since our last Shareholder Update, our primary focus has continued to be on our anticancer drug tigilanol tiglate and advancing the Phase II human clinical trials, building relationships with clinical key opinion leaders, and activities to support and facilitate commercial partnering of the drug.

In parallel, the programme with our wound healing drug candidate (EBC-1013) has also progressed with the completion of the required formal toxicology programme to support a first-in-human study, production of GMP batches of EBC-1013 suitable for human clinical trial use, drafting of a close to final Protocol for the first-in-human safety study in patients with venous leg ulcers, exploratory discussions with potential industry partners, and publication of research to further validate the mode of action of our drug (including its potential use in managing biofilms on implants).

Our discovery programme also continues in the background to identify a pipeline of potential new compounds for treatment of bacterial infections and inflammatory conditions for further evaluation and development when resources and opportunities become available. We are also actively exploring avenues for new commercial collaborations with early-stage product candidates.

1. Human Oncology (tigilanol tiglate)

Clinical trials – soft tissue sarcoma

Patient recruitment of our QB46C-H07 Phase II pilot trial treating soft tissue sarcoma (STS) at the Memorial Sloan Kettering Cancer Center in New York is progressing well. Ten patients are required in this pilot study which opened in late April, with three patients already treated and two more patients screened and consented for inclusion. The first patient has since had two additional tumours treated.

This recruitment rate is impressive considering STS is a relatively rare disease with specific sub-types potentially eligible for orphan drug designation (ODD) with the US Food and Drug Administration (FDA). Based on the results of our ongoing veterinary clinical studies of STS, results from our Phase I/IIa skin and subcutaneous tumours safety trial and initial results from this current human Phase II trial, we are currently preparing an ODD application to the FDA for tigilanol tiglate treatment of STS. Under this designation, if the clinical data from a Phase IIb trial in humans is supportive, registration of the drug can potentially be achieved without the need for a full Phase III trial, there is exemption from company users fees, up to seven years of market exclusivity after approval, and tax credits (https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions).

Clinical trials – head & neck cancer

A final report on our completed Phase I/IIa head and neck squamous cell carcinoma dose escalation safety trial in Australia and India (QB46C-H03) has been prepared by our Chief Medical Officer. Nineteen patients were treated in this "window of opportunity before surgery" trial. The trial successfully met its primary endpoint of safety and tolerability of tigilanol tiglate when administered as a single intratumoural dose.

The drug successfully escalated to a dose level of 2.4 mg/m^2 without any Serious Adverse Events (SAEs) other than an extension of an overnight stay for one patient. Adverse Events (AEs) reported were local and, other than pain, associated with the mode of action (MOA) of the drug in tumour destruction. QBiotics decided to end the trial on the basis of having sufficient safety information to inform our Phase II efficacy study in head and neck cancer (H&NC) which is now open at multiple sites in the UK and Australia.

Overall, tigilanol tiglate treatment was well tolerated at all dose levels in the QB46C-H03 trial, injected tumours demonstrated rapid drug-induced necrosis as expected, with no necrosis reported in the surrounding normal tissue.

In addition, translational research findings from assessment of biopsy samples taken from patients in the study also demonstrated fundamental aspects of the mode of action of the tigilanol tiglate in humans. Samples taken from injected tumours within the first hours following treatment demonstrated the rapid induction of markers of immunogenic cell death, while untreated areas of tumour that were surgically excised between 15 to 21 days later showed a consistent increase in immune cell infiltrate compared to pre-dose samples. These findings of tumour destruction by immunogenic cell death and stimulation

of an immune response in humans are consistent with those observed in animal models and inferred from laboratory data.

Patient recruitment for our current human Phase II H&NC efficacy trial (QB46C-H08) is progressing more slowly than anticipated, with three patients treated to date. In part, this slow recruitment is associated with the current situation with the UK National Health Service (NHS), where the majority of our trial sites are located. The NHS is facing significant challenges from staff shortages, rolling strikes by medical and nursing staff, and substantial patient waiting lists (https://www.nytimes.com/2023/07/16/world/europe/uk-nhs-crisis.html). To address the situation, we have recently opened a second trial site in Australia (the Princess Alexandra Hospital in Brisbane where the lead investigator was also involved in our successful Phase I/II safety study in humans) and are progressing an additional site at Europe's largest cancer hospital, the Gustave Roussy Cancer Centre in Paris, with an internationally recognised clinical team that are expert in intratumoural treatment of cancers. We will continue to closely monitor the progress of this trial in the coming months.

Clinical trials – melanoma

Our two human melanoma clinical trials (i) QB46C-H04 a Phase II tigilanol tiglate monotherapy, and (ii) QB46C-H06 a Phase I/IIa tigilanol tiglate/pembrolizumab (Keytruda®) combination dose escalation safety trial designed in collaboration with MSD (tradename of Merck & Co., Inc., Kenilworth, NJ, USA) were formally closed in February, an analysis of the data is now completed and final study reports in draft.

A total of 4 patients (3 in the combination study and 1 in the monotherapy study) of the planned 52 patients (40 in QB46C-H04 and 12 in QB46C-H06), were recruited during the 20-month period that these trials were open. These patients all had a heavy disease burden and had failed multiple lines of both standard therapies and clinical trial treatments with other experimental drugs/drug combinations (including previous treatments involving pembrolizumab).

In brief, the results from the official study records for QB46C-H06 showed that the combination treatment regime of low dose tigilanol tiglate and pembrolizumab was considered safe and tolerated (i.e., there were no SAEs or systemic AEs) as judged by the Safety Review Committee (clinicians responsible for the safety assessment of the trial data). AEs reported in the trial records were localised to the treatment area and, other than pain, associated with the mode of action of the drug in tumour destruction and initiation of a localised immune response. Tumour necrosis (tumour destruction) was observed for all injected tumours in all 3 patients. For one patient, all injected tumours achieved a Complete Response (full destruction of the treated tumours) with no tumour recurrence at time of withdrawal from study (15 months after treatment). In this patient a non-injected tumour at a distal site had a Partial Response (≥30% reduction) which also lasted for 15 months.

Although the combination study with pembrolizumab has closed, we still maintain a dialogue with MSD.

Injected tumours in the single patient in the monotherapy study (QB46C-H04) necrosed, but because of their close proximity to each other, coalesced to form a large wound area which took several months to heal. Treatment site pain was reported as an AE. The treating physician requested a second treatment (off study under a Special Access Scheme). However, at the time of the second treatment the patient was assessed as having extensive progressive metastatic disease, taken off study and no further information was able to be obtained.

Commercialisation of tigilanol tiglate

We are currently investing significant effort into identifying and securing an industry partner for commercialisation of tigilanol tiglate for human application. We already have a wealth of data from our basic research programme, veterinary clinical studies, and our completed earlier phase clinical trials, which has been compiled to engage with partners while we advance our critical Phase II programme to maximise potential deal value. Since the last Shareholder Update we have:

- Made oral presentations and held initial meetings with potential partners at both Bio-International 2023 (Boston USA) and the 9th Annual SACHS Immuno-Oncology Innovation Forum (Chicago USA), a number of the meetings have resulted in follow up and exchange of further information;
- Held meetings with clinical key opinion leaders and some of our current clinical trial investigators at the American Society of Clinical Oncology 2023 Annual Meeting (Chicago USA);
- Attended the prestigious, invitation-only, Jefferies' Health Care Conference (New York USA);
- Appointed a Chief Medical Officer (Dr Marissa Lim), and a specialist Business Development advisor (Richard Godfrey) with experience in biotech and oncology licensing to strengthen our company's clinical and partnering teams; and,
- Continued to identify target companies based on their product pipelines as well as monitor the deal-making environment.

The close relationships that senior management have built with key clinical opinion leaders in Europe and the USA have also led to valuable direct introductions to a further group of potential partner companies.

2. Veterinary Oncology (STELFONTA®)

Although the market uptake of STELFONTA® is slowly increasing, we continue to closely monitor the overall lower than expected sales of the product, especially in the European market, and are currently reviewing opportunities with marketing partner Virbac to gain greater market traction. STELFONTA® is demonstrably an effective product in the clinic.

The hurdle limiting broader market acceptance appears to be the highly disruptive nature of the drug and its unique mode of action when competing with surgery as the entrenched standard of care. Overcoming this initial adoption hurdle relies on educating general practice veterinarians through the experience of the first one or two treatments as to both the clinical and financial benefits of the drug, at which point there is good evidence of repeat uptake. To this end, we are evaluating more direct means of 'in-clinic' interaction with veterinarians as well as continuing our active education programme to further raise the profile of the drug using key opinion leaders and early adopters in Europe, the UK, the USA and Australia.

In addition, we have recently restructured our internal STELFONTA® support activities and achieved cost savings to improve the commercial viability of the product to QBiotics.

Phase IV post market clinical trials with veterinary oncologists and equine specialists to explore the potential for market expansion for STELFONTA®, as well as to inform our human programme and establish 'pan-tumour' efficacy (i.e., efficacy is not specific to individual tumour types or specific tumour gene mutations), are continuing with encouraging results in canine STS, equine sarcoids and equine melanoma. The most advanced of these studies, an international trial (AU, UK, Spain, Netherlands, Sweden, USA) in treatment of equine sarcoids (a type of papilloma-induced sarcoma), has finalised recruitment and is in the reporting phase.

3. Wound Healing (EBC-1013)

Our wound healing drug candidate (EBC-1013) continues to progress toward a first-in-human Phase I/IIa dose-escalation safety trial in patients with venous leg ulcers in the UK and Australia.

The final reports from the formal toxicology programme required to support the first-in-human study are in late-stage review, the necessary GMP batches of different concentrations of EBC-1013 suitable for human clinical trial use have been produced and lead clinical sites and Principal Investigators in the UK and Australia have been selected.

While a full draft Protocol for the first-in-human study has been available for some time, we decided to seek additional independent review and advice because of the unique nature and mode of action of EBC-1013. Based on this advice, we have further modified the trial design and endpoints, including reducing both the length of the trial and the number of patients needed, while being mindful of satisfying requirements of the regulator and human ethics committees. We anticipate a final Protocol will be submitted to the UK regulator (the Medicines and Healthcare products Regulatory Agency (MHRA)) by the end of September 2023. Unfortunately, consistent with general problems in the UK health system, the MHRA have recently announced that the standard assessment time for clinical trial applications has now been increased from 60 days to approximately 5 months. In parallel, we will proceed with trial initiation in Australia under a Clinical Trials Notification

(CTN) which requires human ethics committee approval and subsequent notification of the Therapeutic Goods Administration (TGA).

In other developments related to our wound healing drug:

- A dose finding study has commenced in canine wounds to inform dose selection and regimens for a future Phase II human efficacy study, with 5 patients treated to date;
- Exploratory discussions have been held about collaboration opportunities with two potential international industry partners; and,
- A scientific publication further demonstrating the antibacterial mode of action of EBC-1013 and exploring its potential use in managing biofilms on implants has been published (Xue W. *et al.* Defining *in vitro* topical antimicrobial and antibiofilm activity of epoxytigliane structures against oral pathogens. *Journal of Oral Microbiology*, 15:2241326).

4. Intellectual Property

We continued to extend protection of our core Intellectual Property around tigilanol tiglate and our wound healing drug candidate EBC-1013 and related analogues. Key patent related activities during the period include the following:

- Granted Patent: Combination therapy for the treatment or prevention of tumours (covering tigilanol tiglate and Immune Checkpoint Inhibitor anticancer drugs) was granted in Europe joining earlier granting in the USA, Japan, Korea, Singapore and other jurisdictions already granted.
- Patent Application: Method of treating tumours (using tigilanol tiglate to generate an abscopal/systemic immune effect in untreated distal tumours) entered National Phase and is now under examination in the USA, Europe and Japan.
- Patent Application: Biofilm disruption (effects of epoxytiglianes in disrupting multidrug resistant Gram-negative bacteria biofilms) entered National Phase and now under examination in US and Europe.

5. Corporate update

The QBiotics Board are in the process of implementing an independent review of the full Board (Non-Executive and Executive Directors) to identify future skills required to guide the company's growth and development, especially related to the listed environment. The review is expected to be completed in time for the company's AGM in November.

In parallel, we continued to build the company's international profile with pharmaceutical industry partners and institutional investors through presentations at biobusiness conferences (see section on commercialisation of tigilanol tiglate).

We also have strengthened relationships with leading brokers and made presentations at Australian investor conferences, for example a keynote presentation by the CEO at the recent Wholesale Investor Venture and Capital Conference in Sydney.

6. Financial update

We are closely monitoring and managing our financial position. As the global financial situation remains somewhat unstable, and biotechnology company share prices remain depressed, we have implemented ways to conserve cash while maintaining focus on value adding milestones such as human clinical development. These measures include reducing internal costs for STELFONTA® activities, reducing travel cost, no salary increases awarded to staff or Directors, and the CEO waiving her right to any personal bonus.

As of 30 June 2023, the company held $59.1 million as cash and term deposits. Cash burn for Q4 FY2023 was $5.3 million, which compares well to the previous quarter (Q3 cash burn was $7.8 million).

We are in the process of finalising the annual report for the year ended 30 June 2023. The unaudited financial results for the year ended 30 June 2023 include:

- Income of $13.6M including (i) $8.6M FY23 R&D Tax Incentive and grants, (ii) $2.5M sales revenue from STELFONTA, and (iii) $2.5M of interest and foreign exchange gains; and,
- Expenses of $35.2M including (i) $13.9M R&D contractors, (ii) $13.3M personnel, and (iii) $8.0M other expenses.

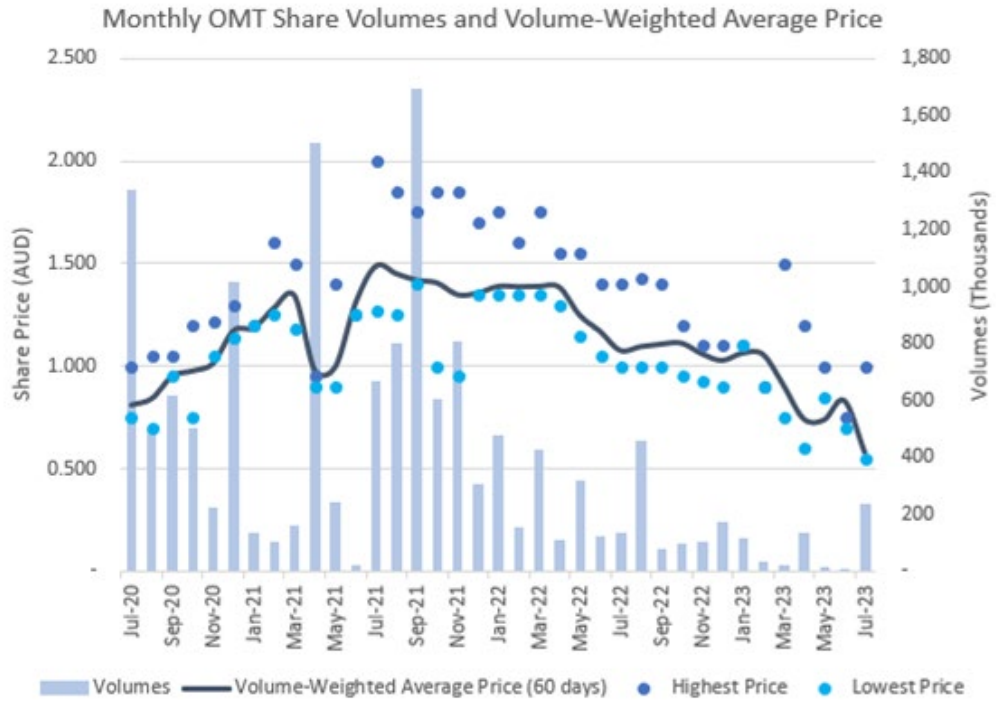
We will notify shareholders once the annual report has been audited and adopted by the Board in early September 2023.

7. Buying and selling QBiotics shares

As shareholders are aware, QBiotics has an Off Market Trading facility for buying and selling shares via a process documented in the Buy & Sell Shares page on the QBiotics website.

As some shareholders find this process laborious, we have investigated various companies who provide a trading platform for unlisted entities. The drawback for this approach is that transactions fees can be up to 6% and only sophisticated investors can buy shares. As we have a significant number of retail shareholders, we are looking into maintaining the current facility as well as engaging with a company to provide access to a trading platform for those who wish to use it. We will inform shareholders as soon as this platform is available. A summary of the recent OMT data can be found in the graph below.

If you have any questions, or require clarification on any of the above, please do not hesitate to contact the company. Shareholder enquires should be directed to QBiotics Group Investor Relations Manager, Ken Pointon. Ken can be contacted by telephoning (07) 3870 8933 or emailing ken.pointon@qbiotics.com. Shareholders are encouraged to view the 'Announcements' page of the Company's website for the latest Company announcements.



Thank you for your ongoing support which underpins all our achievements. Together we are building an extraordinary company. As always, it is a pleasure to share the journey with you.

Yours sincerely,

Dr Victoria Gordon
Chief Executive Officer & Managing Director
QBiotics Group Limited

DISCLAIMER

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