



# Biotech Daily

Friday May 27, 2022

*Daily news on ASX-listed biotechnology companies*

## Dr Boreham's Crucible: Opthea

**By TIM BOREHAM**

**ASX code:** OPT

**Nasdaq code:** OPT (American depositary shares, each equal to eight shares)

**Share price:** \$1.335

**Shares on issue:** 351,939,280

**Market cap:** \$469.8 million

**Chief executive officer:** Dr Megan Baldwin

**Board:** Dr Jeremy Levin (chairman), Dr Baldwin, Michael Sistenich, Lawrence Gozlan, Dan Spiegelman, Dr Julia Haller, Dr Susan Orr, Quinton Oswald

**Financials (half year to December 31, 2021):** revenue \$91,218 (down 54%), loss of \$37.7m (previous deficit \$28.2m), cash \$88.2m (down 43%)

**Identifiable major shareholders:** Regal Funds Management 12.58%, Baker Brothers Life Sciences 8.2%, Jagen Pty Ltd (Liberman family office) 3.3%

The back-of-the-eye disease house is zigging rather than zagging, with its shares lifting more than 30 percent over the last month while the rest of the biotech sector has sagged like a failed sponge.

Do investors have special visionary powers? There's no apparent reason behind the share surge, with first results from the Opthea's phase III registration trial not due to mid-2024.

One likely reason is that Opthea chief Dr Megan Baldwin has been making up for lost Covid lockdown time and has been hitting the (virtual) conference circuit hard.

This month, it was Citi's and HC Wainwright global life science shindig, as well as Retina World Congress in Florida.

In March, Dr Baldwin fronted Oppenheimer's virtual conference and coming up is the Bascom Palmer Eye Institute's Angiogenesis, Exudation and Degeneration 2022 "gath" (which is what the young ones call events these days).

Dr Baldwin notes there's an element of catch-up, in that the shares were hit hard 12 months ago.

"We were trading at a ridiculous valuation for the stage we are at," she says. "So, it's all about letting the market in both the US and Australia know we are in the final stages and getting the word out there."

The final stanza consists of two phase III pivotal trials to assess - or confirm - the efficacy of Opthea's treatment for wet age-related macular degeneration (wet AMD), the biggest cause of blindness for over 60s.

"We are one of the few biotech companies in Australia taking on a phase III asset development," Dr Baldwin says.

### **Opthea's vision statement**

Wet AMD is marked by loss of vision caused by degeneration of the central portion of the retina (the macula).

Blood vessels grow abnormally under the retina, resulting in leakage of fluid and protein from the vessel. The condition can set in quickly, with patients losing their vision in as little as 10 weeks.

A so-called 'trap inhibitor', OPT-302 is a fusion protein that blocks the activity of two proteins, vascular endothelial growth factors C and D (VEGF-C and VEGF-D).

Opthea is developing OPT-302 as a wet AMD combination therapy with the existing drugs Lucentis (ranibizumab) and Eylea (aflibercept), which only block VEGF-A.

About half the market is treated off-label with Avastin, an old cancer drug.

"The existing therapies are no good for 45 percent of patients, because the disease process is more complex than just blocking VEGF-A," Dr Baldwin says. "We are basically targeting a mechanism of resistance to the current standard-of-care treatments, which are blockbuster agents in themselves."

The company is also interested in diabetic macular oedema (DME), but this program has been "paused" after disappointing clinical results (see below).

## **Getting in the rhythm**

Opthea is the renamed iteration of Circadian Technologies - the first ASX-listed biotechnology company.

Founded by biotech doyen Leon Serry, Circadian was “an incubator” for companies including the Victoria state-founded Amrad, (later renamed Zenyth and sold to CSL). Other companies in its portfolio were Metabolic (which became Calzada before morphing into Polynovo), Antisense and Optiscan.

Circadian dabbled in a number of applications including melatonin for jet-lag (hence the name), drugs for Alzheimer’s disease and cancer diagnostics before focusing on eye ailments.

Circadian acquired the VEGF portfolio in 2008 and the company changed its name to Opthea in December 2015. Dr Baldwin was anointed CEO in February 2014, having been at Circadian since 2008 in roles including overseeing the OPT-302 program.

In October 2020, the company launched a US offering of American depository shares, now listed on the Nasdaq Select Global Market.

The company aimed for \$US160 million but ended up raising \$US128 million - which is still nothing to sneeze at ...

## **Clinical trial triumphs and tribulations**

In August 2019, Opthea shares jumped as much as 160 percent after the company released the results of its keenly-awaited phase IIb trial for wet AMD.

The trial enrolled 366 previously untreated patients across 110 sites, testing a combination of Opthea’s OPT-302 with the standard of care therapy, ranibizumab (Lucentis).

The results showed this combined treatment produced “statistically significant and clinically meaningful” results, with a mean “visual acuity gain” after 24 months.

But the biotech gods are fickle: in June 2020 Opthea shares were birched after the company revealed underwhelming phase IIa data from its 144-patient diabetic macular oedema (DME) trial.

Affecting a younger, working age demographic, DME is a blindness-inducing condition that also involves retinal leakage.

Dr Baldwin says the results were unflattering because the patients had been treated with the standard-of-care and were not treatment naïve. This made the visual acuity hurdle harder to surmount.

“It was a noisy data set,” she says. “But when we teased out the patients that had a very consistent anti-VGEF-A treatment with Eylea, we saw the clinical benefit.”

## **What's next?**

Naturally, the market's attention is now focused on the phase III wet AMD trial, which is open in 25 countries across 200 sites.

The company has been recruiting for a year, with patient uptake gaining pace post pandemic.

The two studies, Shore and Coast, are in combination with ranibizumab and aflibercept, respectively. This is to obtain broader approval for use with any type of VEGF inhibitor.

Each trial aims to enrol 990 patients and are sham controlled, triple masked, randomized and all the other things one would expect from a properly constructed clinical program.

While the target patient population is similar, Opthea is boosting its odds of success by not recruiting a non-responsive subset of patients with a lesion called RAP.

RAPpers accounted for about 10 percent of phase IIb patients.

The analysis will also be "enriched" by first assessing the 80 percent patients that fared best in the previous trial. Eventually, though, the whole patient population will be analyzed.

"We are very comfortable with how we have designed it and how we plan to analyze it," Dr Baldwin says.

## **Pretty Chronic for Vision**

While Opthea is not into RAP, it's quite happy to enrol patients with a wet AMD variant called polypoidal choroidal vasculopathy (PCV), by which fluid leaks and bleeds from abnormal blood vessels.

"It means vessels that are ... in the back of the eye grow as polyps," Dr Baldwin says. It is especially prevalent in Asian populations and is said to be the most common form of Wet AMD, globally.

In the phase IIb trial, 18 percent of the 366 treatment-naïve patients had PCV.

After six months, the standard-of-care cohort had a seven-letter improvement on the eye chart, while for those treated with OPT-302 the improvement was almost double (a further 6.7 letters).

Dr Baldwin says the phase III effort should include a similar proportion of PCV patients, or perhaps more, given that more Asian centres are participating.

She says the company possibly could launch a supplemental PCV-specific study, probably in collaboration with Asian experts.

## **Finances and performance**

In the current climate for biotechs, cash is king, so it's heartening that at the end of March Opthea had \$88 million crisp ones in the bank. The not-so-good news is that the company chewed through \$37.7 million in the December 2021 half, with \$31.8 million devoted to research and development.

"Retinal studies are not cheap," Dr Baldwin says. "We have no need to raise capital but we will keep monitoring as we move along."

In February, the company entered an at-the-market equity program, by which the company can sell up to \$US75 million of its ordinary shares in the form of its American depositary shares. The opportunistic arrangement means Opthea can sell shares in dribs and drabs at prices offered by participating buyers - but it doesn't have to.

The amounts raised are likely to be much less than \$US75 million.

Over the last 12 months, Opthea shares have traded as low as 81 cents (March 3 this year) and as high as \$1.67 (June 17 last year). Historically, they peaked at \$3.45 in September 2019 and troughed to 20 cents in June 2015.

## **Biosimilar but different**

Some investors have been concerned about the emergence of biosimilars, which are cheaper copies of existing therapies.

"There's confusion in the market but we do not compete with biosimilars, they help our price point," Dr Baldwin says. "Biosimilars reduce the overall pricing pressure for insurers, which helps us."

"A cheaper version of [existing] therapies means we have a better opportunity of pricing our therapy at a higher value as we can, which is important for a novel and differentiated product."

Opthea is even open to the possibility of acquiring a biosimilar company and co-formulating OPT-302 in the same vial. That way, the standard of care and OPT-302 can be delivered in the one injection.

## **A Kodiak moment worth forgetting**

In February the Nasdaq-listed Kodiak Lifesciences announced that its phase IIb/III trial of its own AMD combination drug candidate, KSI-301, had failed to prove the key intended benefit of requiring less frequent injections into the eye.

As broker Wilsons comments, Kodiak was aiming for a long duration dosing schedule, by which patients would need to be injected only every three to five months.

Inaptly titled Dazzle, the trial was “unable to show non-inferiority to 8-weekly aflibercept (Eylea)” on the eye chart.

In effect, patients needed more doses than expected and Kodiak shares plunged 80 percent on the news.

The results suggest that a new wet AMD treatment needs to show efficacy rather than durability alone.

### **Dr Boreham’s diagnosis:**

Love ‘em to bits and all that, but local investors are known for being a tad impatient. While the 2024 clinical results timeline seems many a sleeps away, it’s not that long in drug development terms.

Broker Wilsons cites a \$US1.5 billion “peak sales opportunity” for the use of OPT-302 as a combination wet AMD treatment.

The company notes that Lucentis and Eylea have revenues in excess of \$US12 billion a year and that’s growing over time with the ageing populace.

“Opthea is the only company with a clinical program that has shown efficacy over and above the existing blockbuster agents,” Dr Baldwin says.

“We are on the verge of blockbuster potential, but it takes time to get there. Our strategy is to keep our eye on the prize of an approvable blockbuster therapy that will improve people’s lives.”

***Disclosure: Dr Boreham is not a qualified medical practitioner and does not possess a doctorate of any sort. But he likes to think of himself as a man of vision – if he can find his damn glasses that is.***