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Circadian Technologies (CIR)

We see Value Clearly

Recommendation

Buy (Initiation)

Price

\$0.20

Valuation

\$0.38 (initiation)

Risk

Speculative

GICS Sector

Pharmaceuticals & Biotechnology

Expected Return

Capital growth	90.0%
Dividend yield	0.0%
Total expected return	90.0%

Company Data & Ratios

Enterprise value	\$11.6m
Market cap	\$30.0m
Issued capital	150.19m
Free float	98.6%
Avg. daily val. (52wk)	\$13,244
12 month price range	\$0.135- \$0.245

Price Performance

	(1m)	(3m)	(12m)
Price (A\$)	0.21	0.15	0.19
Absolute (%)	-9.52	31.03	2.31
Rel market (%)	-2.66	36.21	9.64

Absolute Price



SOURCE: IRESS

Lead asset OPT-302 has blockbuster potential in wet AMD

Circadian is focused on the development and commercialization of angiogenesis-based therapies for the treatment of eye diseases. It's lead asset OPT-302 is targeting wet Age-related Macular Degeneration (wet AMD), the leading cause of vision impairment in the elderly. The drug has a novel mechanism of action and the potential to be useful in other eye disorders.

Current standard of care for wet AMD is anti-VEGF-A therapy. With only three of these drugs used to treat wet AMD, the market is largely untapped and underserved. The 2 approved anti-VEGF-A drugs combined generated ~US\$7bn in revenue in 2014. The multi-billion dollar market, characterised by an unmet need for new therapies that could improve visual outcomes, ensures that biopharmaceutical companies remain on the lookout for promising assets to license.

Preclinical data suggest that OPT-302 used in combination with standard of care anti-VEGF-A therapies has the ability to improve the vision benefits seen with anti-VEGF-A monotherapy in wet AMD patients. This creates a compelling and potentially large commercial opportunity. We model US\$1.5bn peak worldwide sales for OPT-302.

Investment view – Initiate with a Buy and Valuation of \$0.38

We initiate coverage on CIR with a Buy recommendation. We value CIR using a risk adjusted DCF at \$0.38. Our research indicates that the industry is receptive to a combination approach with anti-VEGF-A therapy in wet AMD and sees multi-billion dollar potential in it.

OPT-302 is in a Phase 1/2A trial in wet AMD patients under an FDA approved IND. The Phase 1 trial is due to report in 1QCY16. Successful clinical progress would add value to the asset and allow monetisation through a licensing deal. We forecast that OPT-302 is licensed in 1HCY18 for a deal worth US\$500m, including US\$70m in upfront and near term milestone payments and double digit royalty on sales.

Cash balance of \$18.4m as at end of FY15, allows the company to fund a Phase 1/2A trial and a Phase 2B trial. The company has cash runway to end CY17.

Earnings Forecast

Year end 30th June	2014A	2015A	2016E	2017E	2018E
Revenue (A\$m)	3.7	3.3	1.5	3.4	25.4
EBITDA (A\$m)	-3.9	-6.0	-5.9	-8.6	18.4
NPAT (reported) (A\$m)	-4.0	-5.3	-5.4	-8.2	13.0
NPAT (adjusted) (A\$m)	-4.0	-5.3	-5.4	-8.2	13.0
EPS (reported) (cps)	-8.2	-4.9	-3.6	-5.4	7.6
EPS (adjusted) (cps)	-8.2	-4.9	-3.6	-5.4	7.6
EPS growth (%)	N/A	N/A	N/A	N/A	NM
PER (x)	N/A	N/A	N/A	N/A	2.6
EV/EBITDA (x)	-3.0	-1.9	-2.0	-1.3	0.6
Dividend (cps)	0.0	0.0	0.0	0.0	0.0
Yield (%)	0.0%	0.0%	0.0%	0.0%	0.0%
Franking (%)	N/A	N/A	N/A	N/A	N/A
ROE (%)	-41.8%	-25.8%	-34.0%	-100.0%	46.2%

NOTE: REVENUE INCLUDES R&D TAX INCENTIVE. FY18 REVENUE INCLUDES RISK ADJUSTED UPFRONT FROM LICENSING DEAL FOR OPT-302. EBITDA EXCLUDES OTHER NON-OPERATING INCOME/EXPENSE. SOURCE: BELL POTTER SECURITIES ESTIMATES

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Investment Case

We initiate coverage of Circadian (CIR) with a buy (speculative) recommendation. Our investment thesis is based on:

\$0.38 valuation: We value CIR using a risk adjusted DCF at \$0.38. The valuation is approximately a 90.0% premium to the current share price of \$0.20/sh.

Lead asset OPT-302 has blockbuster potential: Circadian's lead asset OPT-302 is targeting wet Age-related Macular Degeneration (wet AMD), a multibillion dollar market. We model US\$1.5bn peak worldwide sales (pre risk adjustment) for OPT-302 in wet AMD.

Wet AMD represents significant commercial opportunity: Wet AMD is a large market, growing rapidly with an increasing ageing population. Current standard of care is anti-VEGF-A therapy. There are only three approved anti-VEGF-A drugs in the wet AMD market and one which is used off-label. Roche/Novartis' Lucentis and Regeneron/Bayer's Eylea together make up the approved VEGF-A therapy market for wet AMD. **The annual worldwide revenue generated by these 2 approved anti-VEGF-A drugs combined was ~ US\$7 billion** (across all indications) in 2014. The market for wet AMD is largely untapped and underserved which makes it a lucrative market opportunity for CIR to target.

With OPT-302, CIR aims to fill an unmet need in wet AMD: Although the current anti-VEGF-A therapies produce visual outcomes for most AMD patients, visual benefit from them is limited given that ~18-22% of patients continue to lose vision over a course of a year, the majority do not achieve significant visual gain and for most patients the vision decline continues over time. Resistance to anti-VEGF-A therapy also limits clinical benefits. Hence, there remains an unmet need for therapies which could improve visual outcomes.

OPT-302 has a unique mechanism of action, however is targeting a well validated pathway in wet AMD treatment: OPT-302 is a VEGF-C & VEGF-D inhibitor. VEGF-C and VEGF-D are emerging targets for the treatment of wet AMD as they stimulate blood vessel growth and vascular leakage, which are characteristic hallmarks of wet AMD. However, the VEGF/VEGFR pathway in itself is a well validated pathway. We view this as a de-risking aspect for the drug.

Potential exists to expand the use of OPT-302 beyond wet AMD: OPT-302 will initially be developed for the treatment of wet AMD; however it has the potential to be useful across other ophthalmic disorders such as diabetic macular edema, diabetic retinopathy and macular edema following retinal vein occlusion.

Preclinical data gives evidence of single and additive benefits: Preclinical investigations suggest that treatment with OPT-302 alone or in combination with other anti-VEGF-A agents may be an effective wet AMD therapy. We note that CIR used an internationally recognised mouse model of wet AMD, which has served as the backbone for testing antiangiogenic therapies. This gives us comfort around the robustness of the preclinical data generated.

OPT-302 is now in the clinic. CIR is running a Phase 1/2A trial with OPT-302 in wet AMD patients under an FDA approved IND. Results from the Phase 1 trial are expected in 1QCY16. Successful clinical progress would add value to the asset and allow monetisation through a licensing deal in 2018. The company has cash runway to end CY17. Cash balance of \$18.4m allows the company to fund a Phase 1/2A trial and a Phase 2B trial.

Attractive licensing prospects: Our research indicates that the industry is receptive to a combination approach with anti-VEGF-A therapy in wet AMD and sees multi-billion dollar potential in this approach. We forecast that OPT-302 gets licensed in CY18 for a total deal package of US\$500m, including US\$55m in upfront and US\$15m in near term milestone payment. We also expect tiered double digit royalties (15%-22%) to be payable to CIR.

Valuation

We value Circadian using a risk-weighted DCF. DCF is an absolute valuation approach. We believe the DCF valuation is the most appropriate methodology for Circadian and other early stage biotech companies, as it best captures the long-term nature of drug development and commercialization.

Our DCF model uses risk-adjusted revenue numbers based on the probability of success (of reaching the market) assigned to Circadian's lead product OPT-302 for wet AMD. The probability of success we attribute to it is dependent on its development phase. OPT-302 is currently in Phase 1/2A trials for wet AMD.

The revenue driver in our model is OPT-302 for the indication wet AMD. We assume that the asset gets licensed after completion of Phase 2B trials in 1HCY18, with the partner assuming all future development, regulatory and marketing costs and paying upfront and milestone payments to Circadian and royalties on net sales, in return for exclusive worldwide rights to the drug.

Our DCF valuation model is based on a WACC of 19.0%. We assume a terminal growth rate of 1% to arrive at our valuation of A\$0.38/sh for Circadian.

Table 1 - Summary of Valuation

Forecasts	Base case
Enterprise value from DCF (AUDm)	61.2
Add: Cash at end FY16E (AUDm)	15.0
Less: Debt at end FY16E	0.0
Equity value (AUDm)	76.2
Total diluted shares (million)	200.9
Value per share (AUD)	\$0.38
Current Share price (AUD)	\$0.200
Expected Capital Growth	90.0%

SOURCE: BELL POTTER SECURITIES ESTIMATES

Table 2 - CIR -Probability-Weighted Sum-of-parts Valuation Summary

Asset	Stage	First Fiscal Year of sales (Est.)	Peak Market share	Peak Global Sales (US\$m)	Probability of success	Probability adjusted NPV (A\$m)	Value per share (A\$)	% Mix
OPT-302 - Wet AMD	Phase 1/2A	2022	18% of VEGF-A treated patients	\$1,568	14.5%	\$77	\$0.38	100.7%
Other Pipeline/Non-allocated	NA	NA	NA	NA	NA	-\$16	-\$0.08	-20.3%
Cash (EOY 2016E)	NA	NA	NA	NA	NA	\$15	\$0.07	19.6%
Debt (EOY 2016E)	NA	NA	NA	NA	NA	\$0	\$0.00	0.0%
Equity Value						\$76.2	\$0.38	100%

GLOBAL PEAK SALES ARE PRE-RISK ADJUSTMENT AND ROYALTIES.

SOURCE: BELL POTTER SECURITIES ESTIMATES

Table 3 – Deal Assumptions for OPT-302

Asset	Indication	Stage at Licensing	Licensee	Fiscal Year Timing of deal (Est.)	Total Deal Value in USDm (upfront plus milestones)	Upfront (USDm)	Near term milestone payment (USDm)	Other developmental & regulatory Milestones (USDm)	Commercial Milestones (USDm)	Royalty Rate (%)
OPT-302	Wet Age Related Macular Degeneration (wet AMD)	Phase 2B complete	TBC	2018	500	55	15	230	200	18.0%

NOTE: OUR OPT-302 DEAL ASSUMPTIONS ARE CONSERVATIVE REFLECTING ITS EARLY STAGE. IT COULD POTENTIALLY HAVE ADDITIONAL VALUE FOR EACH ADDITIONAL INDICATION THAT THE LICENSEE PURSUES AND BE OF A HIGHER VALUE IF CLINICAL DATA IS BETTER THAN EXPECTED. ROYALTIES ARE LIKELY TO BE TIERED. WE ASSUME A FLAT RATE FOR NOW. NEAR TERM MILESTONE PAYMENT IS WITHIN 6 MONTHS FROM RECEIVING THE UPFRONT PAYMENT.

SOURCE: BELL POTTER SECURITIES ESTIMATES

Upside Risk to our valuation

- **Clinical success will allow for increased probability of success:** We currently assign a 14.5% probability of success (of reaching the market) to OPT-302, given that it's currently in a Phase 1/2A trial. We envisage that completion of the trial with positive results and subsequent advancement of OPT-302 into Phase 2B trials will allow us to assign a higher probability of success and therefore will lead to material upgrades in our numbers.
- **Timing assumption for licensing deal for OPT-302:** We currently assume a licensing deal for OPT-302 in 1H CY18. If OPT-302 gets licensed prior to our estimates, it will be an upside to our valuation.
- **Conservative assumptions to start with in absence of clinical data:** Our market penetration & pricing assumptions and deal size assumptions, are all based on the premise that OPT-302 as a combination therapy with a VEGF-A therapy for wet AMD will be behind a few years to other combination approaches such as Ophthotech's Fovista. Our base assumption at this stage is that OPT-302 shows at least equivalent safety and efficacy to what we have seen in Phase 1/Phase 2 trials with Fovista. In the absence of clinical data from OPT-302 we are conservative in our assumptions at this stage including our assumptions for the deal size for OPT-302. However, if clinical data shows better data for OPT-302 than what has been observed with Fovista, the deal size could be more than double our current estimates.
- **Combination agent positioning assumed:** At this stage we assume that OPT-302 will be used in combination with existing anti-VEGF-A therapies for wet AMD. However, since single agent activity has been observed in preclinical trials, Circadian will explore single agent activity of OPT-302 in the clinic as well. Should clinical data show significant single agent activity of OPT-302, sufficient for it to go head to head against the existing anti-VEGF-A therapies, it could potentially expand the market opportunity for the asset, although the improvement bar is likely to be much higher than as a combination drug. We will revisit our assumptions on the basis of clinical data on OPT-302 as it becomes available.
- **No value included for expanded indications of OPT-302 presently:** At this stage in our valuation, we do not include any value for OPT-302 for expanded indications beyond wet AMD. However, as seen with other anti-VEGF-A therapies in the wet AMD market, we believe that if the drug works for wet AMD, there is high likelihood for CIR or a potential licensee to pursue additional indications such as macular edema following retinal vein occlusion, diabetic retinopathy and diabetic macular edema. This could considerably increase the market opportunity for this asset, in which case it's likely to be a source of considerable upside to our valuation in future.
- **No value assigned for two non-core oncology assets:** We also do not include any value for Circadian's non-core oncology assets namely IMC-3C5 and VGX-100.

IMC-3C5 a VEGFR-3 antibody has just completed a Phase 1 trial in 44 patients with advanced solid tumours and colorectal cancer. Eli Lilly has an exclusive license to intellectual property from Circadian to develop IMC-3C5. We understand Eli Lilly is currently reviewing the program. Circadian has an annual license fee arrangement with Eli Lilly and is expected to receive royalties on sales should the product ever reach the market. If Eli Lilly progresses the clinical development of this asset through to market approval, royalties on sales to Circadian will be a source of upside to our valuation.

VGX-100 is Circadian's internal Phase 2 ready oncology asset earmarked to be out-licensed or sold. It is a VEGF-C antibody which has completed Phase 1A/1B trials in 43 advanced cancer patients both as a monotherapy and in combination with VEGF-A inhibitor Avastin. Cash injection from a licensing deal or sale of this asset will be a source of upside to our valuation.

Overview of AMD market

Age Related Macular Degeneration (AMD) is a progressive disease of the eye and is the leading cause of vision loss in adults over the age of 50 in the western world. It is a disease which manifests in the elderly population and is uncommon in people younger than 55.

AMD is caused by damage to the macula (the small but central portion of the retina at the back of the eye) which causes loss of central vision. The macula is very important for vision as it contains specialised photoreceptor (light-sensing) cells called cone cells which allow a person to see fine details, see objects clearly, recognise colours and also see straight ahead.

According to AMD Alliance International, approximately 30m people worldwide suffer from some form of AMD, including ~10m in the US.

People with AMD are effectively disabled in their day-to-day functions. AMD distorts the acute central vision necessary for daily activities such as driving, face recognition, watching television and reading and can lead to loss of central vision and blindness.

AMD has a significant economic burden. According to a 2010 study sponsored by AMD Alliance International, the worldwide annual direct healthcare system costs of visual impairment due to AMD were estimated at ~\$255bn.

There are two forms of AMD:

- **Dry or non-exudative AMD:** This is the most common form of AMD. In this form the retinal pigment epithelial cells (RPE) which support the photoreceptor cells in the macula break down slowly. This leads to a gradual blurring of central vision. Dry AMD occurs in 3 stages i.e. early, intermediate and advanced. This form of AMD is characterised by the presence of yellow deposits under the retina called drusen and the thinning of the macula. Drusen vary in number and size depending on the stage of the disease. The dry form of AMD turns into the wet form of AMD for some patients. There is no approved medical treatment for dry AMD currently.
- **Wet or exudative AMD:** This form of AMD is less common (~10% of AMD cases) however; it is more severe, accounting for ~90% of AMD-related blindness. Vision loss in patients is rapid in this form. Wet AMD is caused by the growth of new blood vessels at the back of the eye. All cases of wet AMD are considered late stage or advanced. Almost all patients with wet AMD have previously had the dry form of AMD. There are a few approved treatments available for this wet form of AMD. *Circadian is targeting this wet form of AMD, hence we focus only on this form below.*

Wet AMD is a common debilitating chronic disease of the eye

Wet AMD is the leading cause of vision impairment in the elderly

Wet Age-Related Macular Degeneration (AMD) market - Overview

Wet AMD is a late stage retinal degenerative disease which is caused by neovascularization¹ in the eye. Wet AMD or neovascular AMD occurs when the cone cells in the macula stop working correctly and the body in response starts growing new blood vessels to fix the problem. However, these abnormal vessels start to grow in the wrong place under the macula. Also, they are fragile and leak blood and fluids onto and underneath the macula, causing swelling, which further aggravates the problem instead of fixing it. This swelling and leakage of blood and fluids causes more rapid damage to the macula over time which ultimately forms scars that cause deterioration in a person's

¹ Growth or formation of new blood vessels is referred to as neovascularization or angiogenesis.

central vision and leads to permanent blind spots. Hence, if untreated, progressive retinal damage results in irreversible and severe vision loss leading to blindness.

People with wet AMD without adequate treatment find themselves unable to perform daily activities such as driving, reading, recognizing faces and colours. The disease can severely impact a person's independence and mobility and cause social isolation. Patients with wet AMD also suffer psychologically, with depression being a common co-morbidity found in this population. Wet AMD patients are at twice the risk of premature death as those who are not visually impaired, with increased risk of falls and related hip fractures and premature admission to nursing homes.

Wet AMD usually progresses more rapidly than the dry form, and generally leads to more serious vision loss. **Severe sight loss can occur in as little as three months and without treatment, those diagnosed with wet AMD will become functionally blind within two years.**

As per the National Eye Institute, the US advanced AMD prevalence is ~1.8m and is expected to be ~3m by 2020 owing to the rapidly ageing baby boomer population. More than 200,000 cases of wet AMD are diagnosed in the US each year. The wet AMD market is estimated to be more than US\$5bn. Since the disease affects a rapidly growing ageing population we expect this number to grow substantially.

Wet AMD is a multi-billion dollar drug market growing rapidly with the ageing population

Standard of care treatment for Wet AMD and its quality

There is no cure for wet AMD. It is a progressive disease which currently can only be controlled. Current treatment options for wet AMD focus on treating the disease in two ways: a) by sealing off the leaking blood vessels and b) by preventing blood vessels from growing back. The aim of current therapies is to slow or halt the progression of wet AMD i.e. prevent further vision loss. Some new therapies are able to restore some vision if the patients are treated early however, if scarring occurs then the vision loss in the patient is irreversible and none of the current treatments can restore vision in an eye with scars. There are essentially three groups of treatment options available for wet AMD:

- **Anti-angiogenic/anti-VEGF-A drugs:** The advent of this relatively new class of disease modifying drugs has revived drug development in the wet AMD space by pharma and biotech companies. **These drugs are also called anti-VEGF-A drugs and are the first line of treatment or standard of care for wet AMD patients currently.** The drugs, by preventing abnormal blood vessels from growing back, slow down the progression of the disease. Vascular Endothelial Growth Factor-A (VEGF-A) is a protein that induces angiogenesis or neovascularization which is a key factor contributing to the progression of wet AMD. The anti-VEGF-A drugs bind to and inhibit the biologic activity of VEGF-A, thereby preventing the formation of abnormal new blood vessels in the eye.
- **Photocoagulation Therapy:** This was one of the first and only treatment options available for wet AMD for years. It is a hot/thermal laser treatment which works by sealing the leaking abnormal blood vessels in the retina and discouraging their growth. However it cannot selectively target the abnormal blood vessels and therefore damages nearby healthy tissues and cells in the retina as well. This leads to loss of some vision immediately in the wet AMD patient. Also, not all patients with wet AMD qualify for this treatment, making its applicability limited. As a result, with the advent of newer therapy options for wet AMD which do not damage healthy cells, this form of therapy is rarely used now.
- **Visudyne (verteporfin) Photodynamic Therapy (PDT):** This was the first drug therapy approved for the treatment of wet AMD. Novartis got FDA approval for the drug therapy in 2000. Using this therapy leaking blood vessels are sealed off using a cold laser and a light sensitive drug, Visudyne. Compared to photocoagulation therapy, PDT

Anti-VEGF-A drugs are the current standard of care of wet AMD treatment

is better as it does not damage the healthy retinal cells. However, although PDT seals off and stabilises the existing leaky blood vessels in the eye, it does not prevent the formation of new abnormal blood vessels and is therefore unable to halt the progression of the disease. Treatment by this method is also limited as it is useful only for about one-third of wet AMD patients. Due to these factors, its usage frequency has markedly reduced since the advent of anti-VEGF-A drugs.

Major anti-VEGF-A approved drugs in the wet AMD market

There are three approved anti-VEGF-A drugs in the wet AMD market. All three are administered by an injection into the eye (intravitreal injection) and are more efficient if started at the early stages of wet AMD. Treatment by any of these drugs will require a patient to take multiple injections over the course of one to two years. Prior to treatment a patient is typically given an anaesthetic eye drop to numb the eye and also antibiotic drops to prevent infection.

Macugen was a breakthrough treatment for wet AMD

- **Macugen (pegaptanib sodium injection):** Pfizer/Valeant's Macugen was the first anti-VEGF-A drug. It gained FDA approval in December 2004. This first-in-class drug changed the treatment paradigm for wet AMD. Macugen is an aptamer² which is able to bind to extracellular VEGF-A and block its action. A typical treatment regimen with Macugen requires patients to take an intravitreal injection every 6 weeks i.e. ~8 times a year. It was effective in many cases in halting the growth of abnormal blood vessels to stop the progression of the disease; however the drug failed to restore lost vision in the wet AMD patients. In addition, the majority of patients receiving Macugen therapy continued to lose some vision especially if they missed or delayed a dose. Macugen does not bind to all forms of VEGF-A (only selectively blocks the VEGF-A 165 isoform) and is a poor inhibitor, hence is not as clinically effective as the biologic therapies that block VEGF-A, such as Lucentis and Eylea (see discussion on Lucentis and Eylea below). For these reasons Macugen, after enjoying a brief period of glory, was largely replaced by more efficacious VEGF-A inhibitors and never reached the blockbuster status it was expected to attain.

Lucentis revolutionised the wet AMD treatment landscape

- **Lucentis (ranibizumab injection):** Roche/Novartis' Lucentis, although not the pioneer of the anti-VEGF-A class, raised the bar for wet AMD drugs and changed the treatment landscape following its approval by the FDA in June 2006. **Lucentis blocks all isoforms of VEGF-A unlike Macugen.** Its USP (Unique Selling Proposition) which gave it a substantial advantage over Macugen, was that it helped a proportion of wet AMD patients regain some vision that had been lost due to the disease. This was a boon to patients as regaining at least some vision gave a proportion of patients the ability to resume some of their ordinary functions such as driving, which they could not contemplate earlier. Although, we note that for many patients, even if they gained some vision, this did not necessarily mean they were able to resume ordinary activities.

Lucentis generated ~US\$4.2bn in worldwide sales in 2014

Not surprisingly Lucentis soon became the 'gold standard' of wet AMD treatment. Lucentis is a monoclonal antibody fragment which binds to and inhibits the activity of VEGF-A. The dosing regimen for Lucentis approved by FDA is one intravitreal injection every 4 weeks i.e. ~12 times a year, which is the most efficacious, however alternatively Lucentis can be given as monthly injections for first four months followed by one injection every three months or on an 'as-needed' basis. Lucentis soon became a blockbuster drug and Roche went on to gain additional approvals for Lucentis for other ophthalmic diseases such as diabetic macular edema (DME). Lucentis generated worldwide sales of ~US\$4.2bn in 2014 (across all indications).

- **Eylea (afibercept):** Bayer/Regeneron's Eylea is the third VEGF-A inhibitor to be approved by the FDA for treatment of wet AMD and the newest entrant into the market.

² Aptamers are nucleic acid molecules which have high affinity and high specificity to bind to protein targets.

Eylea costs less and requires fewer injections in a year than Lucentis

Eylea generated ~US\$2.8bn in worldwide sales in 2014

Avastin is frequently used off-label for wet AMD

Avastin is a significant competitor for existing and new anti-VEGF-A wet AMD therapies

FDA approved Eylea in November 2011. In clinical trials Eylea was shown to be as effective as Lucentis in improving and maintaining vision in wet AMD patients. Eylea has a dosing interval advantage over Lucentis which is one of the reasons it gained market share rapidly from Lucentis. The FDA recommends a dosing regimen for Eylea of one monthly injection given for the first three months followed by one injection every two months. Eylea also competes with Lucentis on price with a lower price of US\$1,850 per injection vs. US\$2,000 per injection for Lucentis. Bayer has ex-US rights to Eylea on a 50% royalty payment to Regeneron. Following in Lucentis' footsteps Eylea subsequently gained approval for additional ophthalmic indications such as macular edema following retinal vein occlusion and DME. Eylea generated worldwide sales of ~US\$2.8bn in 2014 (across all indications).

Unapproved anti-VEGF-A drug in the wet AMD market

Apart from the above three approved anti-VEGF-A drugs in the wet AMD market, patients with wet AMD also have a fourth drug treatment option. Avastin is an anti-VEGF-A drug from Roche/Genentech approved for cancer therapy and extensively prescribed off-label for the treatment of wet AMD. Avastin is also administered by an injection into the eye and has a similar molecular structure to Lucentis. For this reason Avastin was administered off-label in wet AMD patients and was found to work as effectively as Lucentis.

Due to Avastin being formulated as an intravenous cancer therapy, Avastin costs ~US\$50 per wet AMD dose while Lucentis costs US\$2,000 for one injection, which makes a huge difference in terms of cost of treatment. This is because a patient generally needs to take multiple injections in a year and the disease is chronic. This inexpensiveness of Avastin compared to Lucentis has encouraged its widespread off-label use for wet AMD even though it is not prescribed or approved by FDA for usage in the eye.

This off-label usage led to the National Institutes of Health (NIH) funding a head-to-head large scale clinical study called CATT comparing Lucentis with Avastin in January 2008. Two year study results published in April 2012 showed that Lucentis and Avastin were equivalent in terms of efficacy in treating wet AMD; however Lucentis had a marginally better safety profile (serious adverse events rate of 32% vs. 40% for Avastin).

News of some serious infections in wet AMD patients who were prescribed tainted Avastin processed by compounding pharmacies led to Avastin being banned for retinal use in some US states in 2011. Nevertheless Avastin continues to make a dent into Lucentis' market share and provides significant competition to Lucentis as well as Eylea and any other anti-VEGF-A inhibitor entering the wet AMD market.

Wet AMD – The unmet need

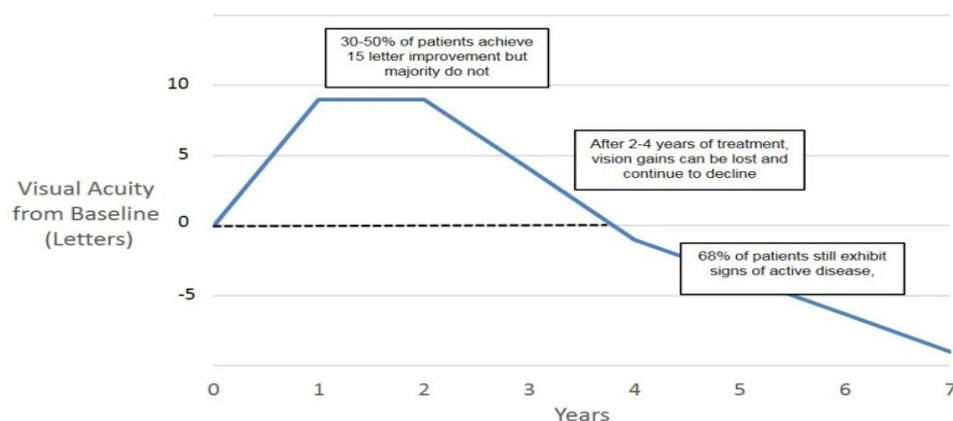
A survey conducted by Decision Resources Group (U.S. and European retinal specialists), found that physicians assign a moderate to high unmet need for new wet AMD therapies that could improve visual acuity (clarity or sharpness of vision) over current standard of care anti-VEGF-A therapies.

Anti-VEGF-A therapies work well for most AMD patients i.e. vision is either maintained or at times improved in patients treated with anti-VEGF-A therapies. However, visual benefit is still limited given that:

- Based on data from clinical trials of anti-VEGF-A drugs (Lucentis and Eylea), after 1 year of treatment with the anti-VEGF-A drug ~18% to 22% of newly diagnosed wet AMD patients still lost additional vision i.e. they lost the ability to read 1 or more letters on a standardized chart used to test vision.
- Similarly, data from the trials also highlight that ~62% to 75% of newly diagnosed wet AMD patients did not achieve a significant gain in vision i.e. an ability to read an additional 15 or more letters on the standardized chart of vision testing. Ability to read 15 or more letters or 3 line gain is considered as significant improvement in visual acuity in previously untreated patients. We note that, the U.S. FDA recommends a statistically significant difference in the proportion of patients with ≥ 15 -letter change in visual acuity, as a clinically relevant outcome measure in wet AMD trials.
- Also, a majority of patients were not able to return to normal (20/20) vision levels. 20/20 vision is a term used to express normal visual acuity measured at a distance of 20 feet. If a person has 20/20 vision, it means that he/she can clearly see letters on an eye chart from a distance of 20 feet that should be seen by a person considered to have normal vision.
- Majority of patients end up progressing over time i.e. their vision deteriorates. A study published in a premier peer reviewed journal Ophthalmology, which assessed visual acuity of patients who received anti-VEGF-A therapy for 4 years (2 years in clinical trials and then additional 2 years at physicians discretion), found that wet AMD patients on anti-VEGF-A therapy remain at risk for substantial visual decline. At the last evaluation in the study, ~46% of patients had lost additional vision i.e. their ability to read one or more letters.

A follow-up study of a cohort of patients from the above study which were assessed 3 years after the above study, showed that ~one-third had poor outcomes i.e. they lost the ability to read 15 or more letters on the chart. In addition ~37% patients had visual acuity at the level of legal blindness (i.e. 20/200 vision).

Figure 1 – Unmet clinical need in Wet AMD market



SOURCE: COMPANY DATA

Therefore, there exists a significant unmet need for therapies on top of anti-VEGF-A drugs, which would either:

- Yield greater gain in visual acuity i.e. ability to read more letters on an eye chart;
- Maintain the visual acuity of a person for a longer time or slow the decline in the vision of patients;
- Increase the proportion of patients achieving normal (20/20) vision;
- Increase the proportion of patients who achieve significant improvement in vision i.e. gain 15 or more letters.

With OPT-302, Circadian aims to fill this unmet need. It is positioning its drug to be used as a combination treatment on top of anti-VEGF-A therapy, to improve the vision in wet AMD patients who are treated with anti-VEGF-A therapy.

The company will also explore single agent activity i.e. OPT-302 as a standalone agent, given that its preclinical investigations so far have demonstrated both single agent and combination activity of OPT-302 in a mouse model of wet AMD.

Whether CIR ends up demonstrating significant single agent activity in clinical trials to justify pursuing the monotherapy route or not, we believe the fact that the drug has some single agent activity in preclinical studies bodes well for potentially much better outcomes when used in combination. We also note that as far as we know, one of CIR's competitors Ophthotech (mentioned below) did not show any single agent activity in preclinical studies.

Combination approach in wet AMD market has precedence

That there is demand for adjunctive therapies has been validated by US based biotech Ophthotech. Ophthotech has an asset with a different mechanism of action to Circadian, however it is following a similar combination therapy approach with anti-VEGF-A therapies.

It's lead asset Fovista, an anti-PDGF drug is currently in Phase 3 trials. Fovista is being positioned to be used in combination with existing anti-VEGF-A therapies to treat wet AMD. In a Phase 2B clinical trial in wet AMD, patients who were administered Fovista in combination with Lucentis had a statistically significant improvement over Lucentis alone. Patients receiving Fovista/Lucentis combination gained 10.6 letters of vision at 24 weeks vs. 6.5 letters gained by patients only on Lucentis i.e. a 62% relative visual benefit over Lucentis alone. We note that Fovista intravitreal injection is given sequentially with Lucentis intravitreal injection.

Regeneron the maker of Eylea also has its own anti-PDGF combo which it has co-formulated with Eylea in a single injection currently in the clinic, although its ~3 years behind Ophthotech's Fovista.

THE INDUSTRY SEES MULTI-BILLION DOLLAR POTENTIAL IN COMBINATION APPROACH WITH ANTI-VEGF-A THERAPY

Novartis who has ex-US rights to market Lucentis, recently entered into an ex-US commercialization agreement with Ophthotech for Fovista worth US\$1.03bn (including US\$200m in upfront payment). The deal includes mid-30% royalty on net sales of Fovista standalone product and a royalty of approximately equal value on sales of co-formulated Fovista products. Ophthotech retains US rights to Fovista.

PHYSICIANS WOULD PRESCRIBE COMBINATION THERAPY WITH ANTI-VEGF-A

According to the Decision Resources survey mentioned earlier, clinicians believe that clinical data seen with Fovista so far suggest that it can partially fulfil the unmet need of improved visual acuity in the wet AMD market. As per Decision Resources, surveyed U.S. retinal specialists expect that they would prescribe Ophthotech's Fovista to ~25% of their wet AMD patients.

OPT-302 – First VEGF-C & D Inhibitor for Wet AMD

CIR's lead drug OPT-302 is an inhibitor of proteins VEGF-C and VEGF-D which promote angiogenesis (formation of new blood vessels) and lymphangiogenesis (formation of new lymphatic vessels). OPT-302 is a soluble form of the vascular endothelial growth-factor receptor - 3 (VEGFR-3).

VEGF-C and VEGF-D are emerging targets for the treatment of wet AMD as they stimulate blood vessel growth and vascular leakage (permeability), which are characteristic hallmarks of several eye diseases including wet AMD and are also associated with disease progression.

OPT-302 will initially be developed for the treatment of wet AMD; however it has the potential to be useful across other ophthalmic disorders such as diabetic macular edema, macular edema following retinal vein occlusion and diabetic retinopathy.

Overview of the VEGF/VEGFR pathway

The VEGF/VEGFR pathway is recognised as the most important signalling pathway for blood vessel development and vascular leakage. Since many diseases are characterised by a disorder of the vasculature such as cancer and eye diseases, the VEGF/VEGFR signalling pathway has been a target for therapies across a variety of therapeutic indications.

There are two primary strategies for inhibiting the VEGF/VEGFR pathway. These include either targeting the VEGF receptors or targeting the VEGF ligands (proteins).

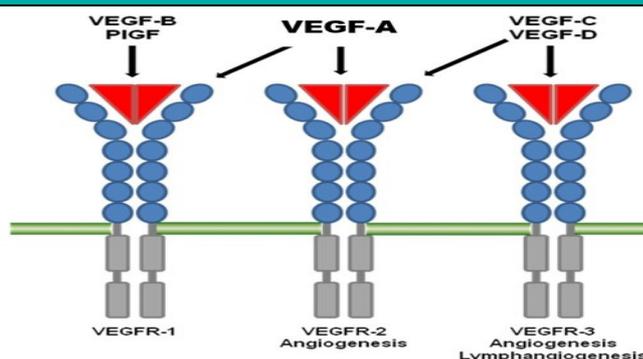
The VEGF family consists of VEGF-A, VEGF-B, VEGF-C, VEGF-D and PlGF (placental growth factor) and their receptors VEGFR-1, VEGFR-2 and VEGFR-3.

The VEGF ligands bind in a partially overlapping pattern to the three tyrosine kinase receptors (VEGFRs) present on the surface of endothelial cells. However, they bind with differing selectivity and therefore have specific roles in regulating the development of blood vessels.

VEGFRs bind with VEGFs, are activated and then initiate a signal cascade that stimulates blood and lymphatic vessel growth (angiogenesis and lymphangiogenesis respectively) and vessel leakage.

VEGF-A has been established as the prime angiogenic molecule. VEGF-C and VEGF-D are primarily lymphangiogenic factors but they also induce angiogenesis and VEGF-C in particular is known to increase vascular permeability.

Figure 2 - VEGF family ligands and their receptors



SOURCE: COMPANY DATA

VEGF-A binds to VEGFR-2 and VEGFR-1 receptors. VEGFR-2 is the primary receptor transmitting VEGF-A, VEGF-C and VEGF-D signals in endothelial cells and therefore is the main pathway driving blood vessel growth. It is for this reason that the development of angiogenesis inhibitors has focused on the VEGF-A/VEGFR-2 system both in the treatment of eye diseases such as wet AMD and in the treatment of various cancers.

VEGF-C and VEGF-D bind to VEGFR-2 and VEGFR-3 receptors. These proteins induce lymphangiogenesis via activation of VEGFR-3. They induce angiogenesis via activation of both VEGFR-2 and VEGFR-3. They increase blood vascular permeability via activation of VEGFR-2.

Mechanism of Action of OPT-302

Activation of the three tyrosine kinase receptors (VEGFRs) is controlled by the binding of the VEGF ligands.

OPT-302 is a soluble form of the vascular endothelial growth-factor receptor -3 (VEGFR-3). It acts as a VEGF-C/VEGF-D inhibitor or 'trap'. OPT-302 being a soluble VEGFR-3 receptor, binds to VEGF-C and VEGF-D proteins and prevents them from interacting with the original target receptors (VEGFR-2 and VEGFR-3).

OPT-302 binds VEGF-C and VEGF-D with very high affinity and competes with the native receptors VEGFR-2 and VEGFR-3 for binding to these ligands. This is why it effectively blocks the 2 proteins from binding and activating the native receptors.

Blockade of the interaction of VEGF-C and VEGF-D with the receptors can inhibit the abnormal blood vessel formation and the vascular leakage in wet AMD.

OPT-302 is similar in structure to Regeneron/Bayer's Eylea. Eylea has been called a VEGF-Trap, because it acts as a soluble receptor that binds to VEGF-A and PIGF preventing them from binding to native VEGFR-1 and VEGFR-2 receptors.

VEGF-C and VEGF-D – emerging targets for Wet AMD

The strategy to target a member of the family of proteins in order to inhibit the VEGF/VEGFR pathway in wet AMD is not new and has several successful precedents.

In terms of wet AMD the strategy primarily used to inhibit the VEGF pathway is through targeting the VEGF-A ligand. The standard of care for wet AMD i.e. Lucentis, Eylea and Avastin all bind to VEGF-A, thereby blocking its interaction with VEGFR-2 & VEGFR-1, which leads to inhibition of endothelial cell proliferation, survival and vascular permeability. Eylea also inhibits PIGF.

However, none of the existing wet AMD therapies block VEGF-C or VEGF-D. **The rationale for targeting VEGF-C and VEGF-D as a target for wet AMD drug development has its basis in the following:**

- Even though VEGF-A inhibitors prevent activation of VEGFR-2 signalling by VEGF-A, VEGF-C and VEGF-D can still activate VEGFR-2 signalling and therefore promote angiogenesis. We note that VEGF-C and VEGF-D induced angiogenesis via activation of VEGFR-2 have been implicated in mediating resistance to anti-VEGF-A monotherapy. Hence, complete blockade of VEGFR-2 requires blockade of all 3 ligands. We note that VEGFR-2 is the primary receptor that drives signals for angiogenesis.
- Selective VEGF-A inhibitors have no impact on VEGFR-3 signalling. VEGFR-3 is activated by binding to VEGF-C and VEGF-D only. Given that VEGFR-3 is also implicated in the growth of blood vessels, preventing its activation should lead to further inhibition of angiogenesis. In the cancer setting, it was found that stimulation of VEGFR-3 augmented VEGF-A induced angiogenesis. It was also observed that

activation of VEGFR-3 sustained angiogenesis even in the presence of VEGFR-2 inhibitors. Researchers have also found that antibodies against VEGFR-3 and VEGFR-2 in combination resulted in additive inhibition of angiogenesis and tumour growth.

- Recent progress in research in the field has also demonstrated the role of VEGF-C and VEGF-D in the pathophysiology of wet AMD. There is evidence that circulating blood plasma levels of VEGF-C are markedly elevated in wet AMD patients. It has also been observed that inhibition of VEGF-A by drugs such as Avastin and Eylea, have been accompanied by upregulation of VEGF-C and/or VEGF-D.

It follows that combining VEGF-A inhibitors with an agent like OPT-302 (VEGF-C and VEGF-D inhibitor), which targets both independent and overlapping pathways with VEGF-A, may achieve a complete blockade of the VEGF/VEGFR signalling, given that both the VEGFR-2 & VEGFR-3 receptors will not be activated. This complete blockade of VEGFR-2 and VEGFR-3 signalling may have the potential to improve the treatment benefits seen in wet AMD patients than what has been achieved so far by targeting VEGF-A alone.

Hence, with OPT-302, Circadian is exploring an emerging target for wet AMD drug development. However, the VEGF/VEGFR pathway Circadian is targeting is a well validated pathway associated with wet AMD.

OPT-302 – The benefits observed in preclinical studies

Preclinical investigations (in a mouse wet AMD model) showed that OPT-302, as a single agent, can reduce wet AMD lesion size and vessel leakage to a comparable extent as Regeneron/Bayer's anti-VEGF-A therapy Eylea. Data also showed that the combination therapy of OPT-302 with Eylea, was more effective in inhibiting wet AMD lesions than either agent alone. The study suggests that OPT-302 has the potential to be used as a single-agent (monotherapy), or in combination with existing standard of care anti-VEGF-A therapies.

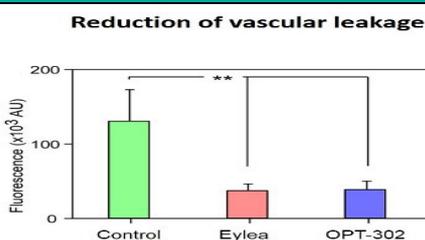
Data from a preclinical study of OPT-302 which underpinned the company's decision to progress the compound into the clinic and formed part of its IND (Investigational New Drug) submission to the FDA, was presented in May 2015 at the annual ARVO (Association for Research in Vision and Ophthalmology) meeting. The ARVO meeting is one of the major ophthalmology conferences in the US.

We note that this study used an internationally recognised mouse model of wet AMD. The mouse model of laser-induced choroidal neovascularization (CNV) has been used extensively in wet AMD studies. Since this model recapitulates the main features of wet AMD in humans, it has served as the backbone for testing antiangiogenic therapies. The preclinical studies were also conducted independently in multiple research laboratories around the world. **Both the above factors give us comfort around the robustness of the preclinical data generated.**

Key conclusions from the study presented at ARVO were as follows:

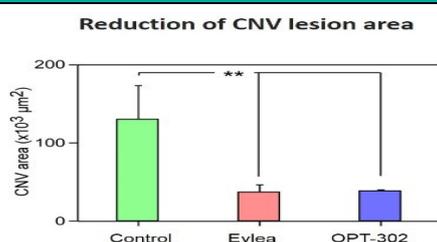
- OPT-302 was effective in inhibiting laser-induced CNV and vascular leakage to a comparable extent as Eylea.

Figure 3 - Reduction of vascular leakage



** P<0.05. SOURCE: COMPANY DATA

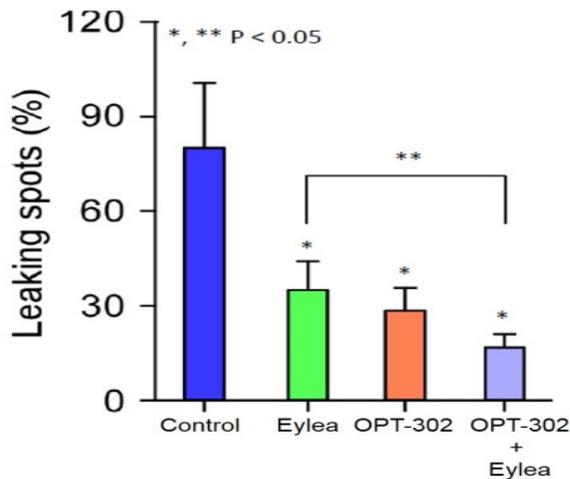
Figure 4 - Reduction of CNV lesion area



** P<0.05. SOURCE: COMPANY DATA

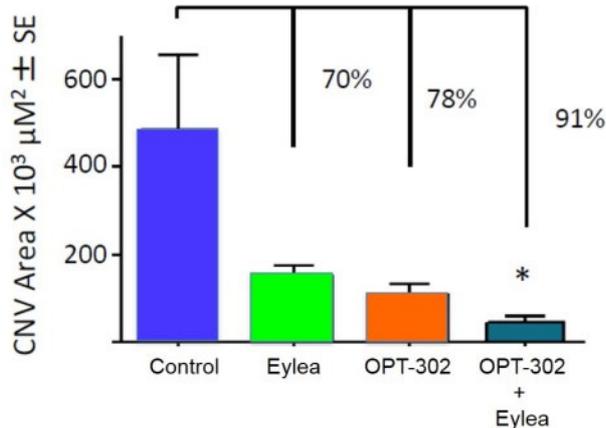
- Combination of OPT-302 and Eylea demonstrated superior inhibition compare to either agent alone.

Figure 5 - OPT-302 combination with Eylea more effectively reduces vascular leakage CNV than either agent alone



SOURCE: COMPANY DATA

Figure 6 - OPT-302 combination with Eylea more effectively inhibits CNV than either agent alone



SOURCE: COMPANY DATA

Hence, in summary the findings from the preclinical study suggest that treatment with OPT-302 alone or in combination with other anti-VEGF-A agents such as Eylea may be an effective wet AMD therapy, particularly in clinically resistant cases of wet AMD.

IND approval by FDA a vote of confidence

The US FDA approved Circadian’s Investigational New Drug (IND) application in June 2015 to initiate its Phase 1/2A trial of OPT-302 in patients with wet AMD. The IND was approved based on preclinical data (safety/toxicology and pharmacological activity), information on manufacturing processes and the Phase 1/2A trial protocol.

Having the IND approved implies that the FDA is satisfied on the following points:

- Preclinical data gathered by Circadian suggests that OPT-302 is reasonably safe for testing in humans.
- Circadian can adequately produce and supply consistent batches of the drug for clinical use.
- The design of the trial and the qualifications of the clinical investigators are up to the mark.

Given that this is the first time FDA has gone through all of the above with relation to OPT-302, we are encouraged that Circadian’s preclinical data, manufacturing processes and clinical trial protocol have passed FDA’s scrutiny.

Since, Circadian’s Clinical Advisory Board and other advisors played an important role in helping the company design its Phase 1/2A trial, we also see the IND being approved without any apparent hiccups as a testimony to the experience and expertise of internal management and people advising the company.

Development path forward for OPT-302

OPT-302 is now in the clinic. Circadian, through its wholly owned subsidiary Opthea Pty Ltd. is currently running a Phase 1/2A trial with OPT-302 in wet AMD patients. The trial is currently enrolling patients in the Phase 1 cohorts. Enrolment into the Phase 2A cohorts will occur under the same trial protocol and following completion of enrolment into the Phase 1. Subsequently, CIR plans to run a Phase 2B trial with OPT-302 in wet AMD patients. Positive results from these trials should add value to the asset and allow monetisation through a licensing deal in 2018. We give a brief overview of the design and endpoints of the trials below:

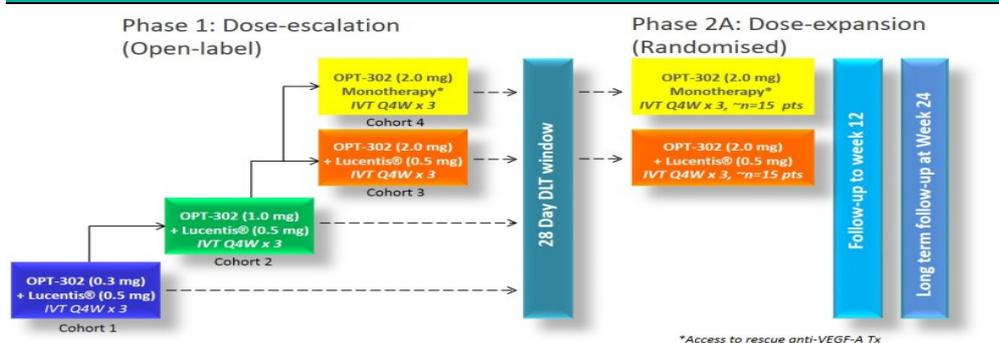
Phase 1/2A trial summary

Start Date: Phase 1 trial initiated on 1st July, 2015. Phase 2A to initiate after the completion of Phase 1 dose escalation cohorts (BPe CY1H16).

Expected timeline for release of Top Line Results: Results from Phase 1 trial expected in 1QCY16 and Phase 2A in 2HCY16.

Trial Design: The Phase 1/2A trial is essentially one trial broken up into two parts. The first part of the trial or Phase 1 is the dose escalation phase and the second part of the trial or Phase 2A is the dose expansion phase. The Phase 1/2A trial design is depicted in the figure below:

Figure 7 - OPT-302 Phase 1/2A trial design



SOURCE: COMPANY DATA

Summary of Phase 1 Trial Protocol:

- Open label, sequential dose escalation study, to evaluate safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of OPT-302 administered by intravitreal (IVT) injection either alone or in combination with Lucentis (ranibizumab) in male and female patients with wet AMD (age \geq 50 years).
- The trial will recruit ~20 wet AMD patients who are either treatment naïve (have not been treated previously) or who have been previously treated with an anti-VEGF-A therapy but demonstrated a sub-optimal response to that prior treatment.
- There will be 4 treatment cohorts. Each treatment cohort will have 5 subjects. The patients in the first three dose cohorts will receive one of three escalating doses of OPT-302 (0.3mg, 1.0mg and 2.0mg) in combination with 0.5mg of Lucentis. The fourth dose cohort patients will receive the highest dose of OPT-302 alone without Lucentis. Patients in the fourth dose cohort will have access to rescue anti-VEGF-A therapy should the need arise.
- Dosing will be once every 4 weeks for 3 months. OPT-302 and Lucentis will be given as sequential injections. OPT-302 IVT injection will be given after a 30 minute gap of the patient receiving the Lucentis injection at each monthly visit.

- The dose-limiting toxicity (DLT) window is 28 days. If a DLT occurs within the 28 day window, 3 additional subjects will be enrolled in that cohort.
- Patients will have initial follow up at week 12 and will have the option of a long term follow up at week 24.

Summary of Phase 2A Trial Protocol:

- Randomised, dose expansion study, to evaluate safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of OPT-302 administered by intravitreal (IVT) injection either alone or in combination with Lucentis (ranibizumab) in male and female patients with wet AMD (age \geq 50 years). Outcome assessors will be masked i.e. will not be privy to whether a patient got monotherapy or combination.
- This is dependent on successful completion of the Phase 1 or dose escalation part of the trial. It is essentially an expansion of cohort 3 and cohort 4 from the Phase 1 trial.
- The highest dose of OPT-302 tested in Phase 1 i.e. 2.0mg or the Maximum Tolerated Dose (MTD) identified in Phase 1 will be the single OPT-302 dose used in the Phase 2A trial.
- The trial will recruit ~30 wet AMD patients who are either treatment naïve (have not been treated previously) or who have been previously treated with an anti-VEGF-A therapy but demonstrated a sub-optimal response to that prior treatment.
- There will be 2 treatment cohorts. Each treatment cohort will have ~15 subjects. Patients will be randomised to receive either OPT-302 alone or OPT-302 in combination with 0.5mg of Lucentis. Patients in the OPT-302 monotherapy cohort will have access to rescue anti-VEGF-A therapy should the need arise.
- Dosing will be once every 4 weeks for 3 months. OPT-302 and Lucentis will be given as separate injections. OPT-302 IVT injection will be given after a 30 minute gap of the patient receiving the Lucentis injection at each monthly visit.
- Patients will have initial follow up at week 12 and will have the option of a long term follow up at week 24.

Sites: The Phase 1 trial is a multi-centre study, being conducted at 5-10 clinical sites in the US under an FDA approved IND.

Primary end-point: Safety and tolerability of multiple ascending doses of OPT-302 IVT injection alone and in combination with Lucentis in wet AMD patients. The time point for primary analysis is Day 28.

Secondary end-points:

- Mean change in best-corrected visual acuity (BCVA) from baseline using eye charts.
- Mean change in choroidal neovascular (CNV) lesion area from baseline (measured by fluorescein angiogram).
- Mean change in central retinal thickness from baseline (measured by spectral domain optical coherence tomography i.e. SD-OCT).
- Pharmacokinetic profile of OPT-302.

SOME POINTS FOR DISCUSSION ON THE PHASE 1/2A TRIAL

Some aspects of the trial warrant further discussion as we detail below:

Benefits of two phase protocol

Generally, for trials which have two phase protocols such as the one Circadian is using, the dose escalation phase would identify initial MTD (maximum tolerated dose). In the dose expansion phase, a cohort of patients will be treated at the MTD or highest dose tested in the dose escalation phase. In the dose expansion phase, the company explores additional safety profile of the drug at the MTD or highest dose tested with a higher number of

patients, so that a more efficient and accurate dose is selected for Phase 2 trials. The benefits for Circadian of using the two phase protocol in our view are twofold:

- Having more patients (~15 planned per cohort) in the dose expansion phase on the MTD dose, gives a reasonable chance for the company to get some preliminary signals of clinical benefit.
- For any novel therapy which has not been previously tried in humans, in the initial dose escalation phase clinicians may have more pre-treated patients with sub-optimal response rather than treatment naïve patients. However, once safety and tolerability is established in the dose escalation phase and a MTD identified, we believe clinicians will be more open to putting treatment naïve patients on the new drug. Since it is important for Circadian to evaluate the effect of OPT-302 on both treatment naïve and pre-treated patients as early as possible in the development path, we believe the dose expansion phase with larger size cohorts is likely to have a better mix of treatment naïve and pre-treated patients, which would give Circadian a higher chance of identifying patterns if any exist.
- Similarly the larger size of the cohorts in the dose expansion phase (15 vs 5 in dose escalation), will also give a better chance to Circadian to observe any apparent signals of monotherapy activity of OPT-302. Hence, results from the dose expansion phase will guide the Phase 2B trial design.

Circadian is using eye charts as well as sophisticated imaging techniques to ascertain preliminary activity

While eye charts are being used to ascertain any improvement in visual acuity (i.e. how many letters a person gains after treatment from their baseline), Circadian is also using sophisticated imaging techniques such as spectral domain-OCT and fluorescein angiogram to determine the change in central retinal thickness and the size of the wet AMD (choroidal neovascular - CNV) lesion area.

When it comes to vision, while improvement in visual acuity is the most important efficacy parameter, decrease in retinal thickness and reducing size of CNV lesions are other surrogate markers which could suggest response to a treatment.

We note that in wet AMD increased retinal thickness is due to fluid build-up from leakage from the abnormal blood vessels. Reduction in retinal thickness has been correlated with improvement in visual acuity. Hence, it is understood that an effective wet AMD drug should reduce retinal thickness from baseline.

Also, formation of CNV in wet AMD is considered to be a determining factor in vision loss in wet AMD. Hence it is reasonable to expect that inhibiting the new blood vessel formation and regression of existing blood vessels (i.e. reduce size of CNV lesion) could reduce the risk of vision loss.

Hence, in our view, if OPT-302 as an add on therapy with Lucentis is able to show reductions in the size of CNV lesions and reduction in retinal thickness, it will clearly indicate that the drug has biological activity. We are also hopeful to observe some improvement in visual acuity even though the trial is not powered to provide statistically significant data.

WHAT WILL WE BE LOOKING FOR FROM THE PHASE 1/2A TRIAL?

- The first and foremost parameter of interest to us will be safety and tolerability given this is the first-in-human clinical trial of OPT-302. We would want to see a clean safety profile, without any dose-limiting toxicities. Ocular adverse events in such a trial could be drug related or associated with the intravitreal injection. Ideally we would not want to see any drug related adverse events. We do expect to see adverse events related to the intravitreal injection, however as long as they are not serious (\geq Grade 3) it should be acceptable.

- We expect the trial will identify the MTD of OPT-302 or establish that the highest dose tested is tolerable. This will establish the OPT-302 dose to be used in a subsequent Phase 2B trial.
- Notwithstanding the small sample size and the lack of a control group which is typical of a Phase 1 trial, we would look for preliminary clinical evidence of an additive benefit of combining OPT-302 with an anti-VEGF-A therapy. We view the Phase 2A dose expansion part as an opportunity to show biological impact.
- To ascertain clinical benefit, when analysing the results from the Phase 1/2A OPT-302 trial, we will pay attention to any observed improvement in the functional endpoint of visual acuity foremost. However, given the small sample size we expect that the SD-OCT and angiography imaging are likely to provide more meaningful data regarding physical endpoints of change in retinal thickness and size of CNV lesions. If the data demonstrates reduction in retinal thickness and regression in CNV lesions from OPT-302 treatment, it will indicate that the drug has pharmacological activity.
- We would also look for any patterns which may emerge on effect of OPT-302 combination on treatment naïve vs. pre-treated patients.
- We will also look to see if there is any signal of pharmacological activity from the OPT-302 monotherapy arm which may warrant further exploring of OPT-302 as a single agent.

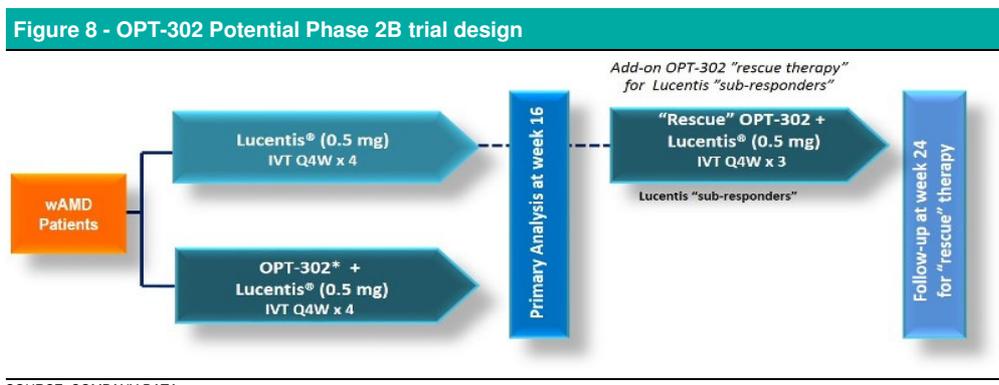
Phase 2B trial summary (Planned)

While the design of a Phase 2B trial with OPT-302 will be finalized based on the findings from the Phase 1/2A trial, at this stage Circadian envisages that a Phase 2B trial would be designed similarly to that described below:

Start Date: After the completion of Phase 2A dose expansion trial (BPe CY4Q16).

Expected timeline for release of Top Line Results: BPe end CY2017.

Possible Trial Design: The Phase 2B trial is essentially going to be an efficacy study with a control arm comparing the OPT-302/Lucentis combination treatment with Lucentis monotherapy treatment. It may also have an extension sub-study in which OPT-302/Lucentis combination therapy will be given as a rescue therapy to patients who were sub-responders in the Lucentis monotherapy arm. The Phase 2B trial design is depicted in the figure below:



SOURCE: COMPANY DATA

Summary of Phase 2B Trial Protocol:

- Randomised, controlled, double-masked, single dose study, to evaluate effects of OPT-302 administered by intravitreal (IVT) injection in combination with Lucentis (ranibizumab) vs. Lucentis monotherapy in patients with wet AMD (age \geq 50 years).
- The trial will recruit only wet AMD patients who are treatment naïve (have not been treated previously). These patients would be newly diagnosed with wet AMD.

- There will be 2 arms in the trial. Patients will be randomised to receive either a single dose of OPT-302 in combination with 0.5mg of Lucentis or Lucentis 0.5mg alone.
- The OPT-302 dose will be decided after the Phase 1/2A trial results are available.
- Dosing will be once every 4 weeks for 4 months. OPT-302 and Lucentis will be given as separate injections. OPT-302 IVT injection will be given after a 30 minute gap of the patient receiving the Lucentis injection at each monthly visit.
- Primary analysis point will be at week 16 for all patients.
- There will also be an extension sub-study in which OPT-302/Lucentis combination therapy will be given as a rescue therapy to patients who were sub-responders in the Lucentis monotherapy arm. In this part of the study the dosing will be once every 4 weeks for 3 months. Patients in the sub study will have follow up at week 24.

Potential end-points of the trial:

- Mean change from baseline in visual acuity, central retinal thickness, fluid & CNV area.
- Safety including both systemic and ocular adverse events.
- Pharmacokinetics.
- Identification of biomarkers for better response to treatment.

SOME POINTS FOR DISCUSSION ON THE PHASE 2B TRIAL

Some aspects of the proposed trial warrant further discussion as we detail below:

- **Size of trial:** At this stage we do not know how big the Phase 2B trial will be. Ophthotech had ~449 patients in its Phase 2B trial of Fovista. However that trial had 3 arms and tried 2 doses of Fovista. As far as we know, this was one of the largest Phase 2 trials in this setting with very high statistical powering. Hence, we expect that the Circadian trial will be relatively smaller to Ophthotech's, with around 200 patients. However, we note that if the Phase 1/2A trial results identify compelling monotherapy activity of OPT-302, it is possible for Circadian to add another monotherapy arm in the Phase 2B trial, in which case the trial size may increase beyond 200 patients.
- **Including a control arm is prudent:** Testing the OPT-302 combination therapy against the anti-VEGF-A monotherapy control group is the most acceptable way to evaluate the efficacy of the combination treatment as the goal is to show superiority over the single agent standard of care. FDA will typically require at least two separate phase 3 trials of OPT-302 combination therapy with an active control arm (i.e. comparing it to a leading marketed drug such as Lucentis), in order to approve it. Circadian views the completion of Phase 2B as an ideal time to license OPT-302. Hence, using an active control in Phase 2B will likely allow early detection of efficacy in the clinic and allow a potential partner to make a more informed assessment of the potential additive activity of OPT-302.
- **Sub-study a smart de-risking strategy:** We believe that CIR's inclusion of a sub study in the Phase 2B trial to determine effect of the OPT-302 combination therapy on Lucentis monotherapy sub-responders is of strategic significance. The way the trial is designed will allow Circadian to explore the effect of OPT-302 combination therapy both on the treatment naïve population and also on the pre-treated population. Benefits seen in both the segments could expand OPT-302's label. Also, we note that usage of an approved combination therapy in a wet AMD patient will ultimately be the prerogative of the clinician. Given the obvious fact that a combination therapy is likely to cost more than a single agent therapy, we believe the clinician will exercise their judgement more frequently for treatment naïve patients. However, for pre-treated patients who are sub-responders, using the combination therapy which makes a label claim of benefiting these patients may very well be a no-brainer for the clinician.

Competing drugs in development

Lucentis' and Eylea's success has attracted other players to the wet AMD market. The blockbuster potential for any novel therapy for this largely underserved market is huge.

Emerging therapies for wet AMD generally can be grouped into three broad headings based on their strategic focus. These include:

- Agents which target anti-VEGF-A but are attempting to extend the duration interval between injections i.e. reduce the number of injections in a year. We note that Bayer/Regeneron's Eylea is one such successful approach. Others who fall in this category include gene therapy approaches and the Allergan/Molecular Partner's DARPin product abicipar.
- Agents which are targeting novel anti-angiogenic targets such as Circadian's OPT-302 and Ophthotech's Fovista.
- Agents which are targeting immune or inflammatory pathways.

The future of ocular gene therapies which were seen as promising until recently, is now uncertain following the high profile failure of Avalanche Biotechnologies Phase 2A trial with its gene therapy product AVA-101.

We are also sceptical about the potential efficacy of emerging oral and topical agents for wet AMD such as Tyrogenex's oral agent X-82 and Ohr Pharma's topical agent OHR-102 which failed to meet its primary endpoint in a phase 2 trial.

Of the emerging therapies the anti-PDGF agents currently garner the most attention and are likely to compete with Circadian for market share.

In our view, there are a few agents currently in development which are promising and worth highlighting apart from Circadian's OPT-302. These include Ophthotech's anti-PDGF agent Fovista, Regeneron's co-formulation of anti-PDGF with Eylea (REGN2176-3), Regeneron's co-formulation of an ANG2 antibody with Eylea (REGN910-3) and Actavis/Molecular Partners DARPin platform with drugs abicipar and a dual targeting anti-PDGF/anti-VEGF-A DARPin molecule.

To our best knowledge, Circadian's OPT-302 is the only molecule which is targeting VEGF-C & VEGF-D in development for wet AMD. Hence, we believe OPT-302 will be unique based on its mechanism of action.

We present a broad overview of selective emerging agents in development for wet AMD in the table below.

Table 4 - Overview of selective emerging wet AMD drugs in development

Company	Drug	Target	Development Stage	Administration	Comments
Ophthotech/Novartis	Fovista	Platelet-derived growth factor beta (PDGF-B)	Phase 3	Intravitreal injection	Positioned as add on therapy to be used with anti-VEGF-A injections. Phase 2B study data indicates that Fovista+Lucentis combination led to greater improvement in vision compared to Lucentis alone at 24 weeks (10.6 letter gain with combination vs. 6.5 letter gain with Lucentis). Based on Phase 2B data, the company inked a \$1.03bn deal with Novartis for ex-US rights only. We expect Fovista to get approval and launch in the US in 2H17, subject to successful Phase 3 trials.
Regeneron/Bayer	REGN2176-3	PDGF-B+VEGF-A	Phase 2	Intravitreal injection	Co-formulation of PDGF antibody with Eylea. This has been granted fast-track designation by the FDA. A 500 patient Phase 2 trial was initiated in April 2015 to compare the effect of the combo product on vision acuity vs. Eylea monotherapy. The trial is being conducted across multiple sites in US and Japan. Phase 1 (12 patient) trial showed no DLT or treatment related AES. Visual acuity was stable or increased in a majority of patients. Central retinal thickness decreased in all the 4 dose cohorts of the combo in the trial.
Molecular Partners/Allergan (now Actavis)	Abicipar (long acting DARPIn)	VEGF-A	Phase 3	Intravitreal injection	This product is focusing on reducing the frequency of injections into the eye vis à-vis current approved anti-VEGF-A products. We note that so far Eylea has been the only real success of this approach. The product faces a high bar since it has to successfully differentiate itself from Eylea. Phase 2b data suggests that abicipar could be administered every 12 weeks following loading doses, compared to every 4 weeks for Lucentis.
Avalanche Biotechnologies	AVA-101 (Gene therapy)	VEGF-A	Phase 2A complete. Immediate plans for Phase 2B shelved	Subretinal	The company's \$102m IPO in 2014 was much talked about along with its \$640m deal with Regeneron. After posting disappointing results from a Phase 2A study in June 2015, the gene therapy company decided to shelve its immediate plans for further studies. Key failure of the study was that instead of meeting its secondary goal of reducing central retina thickness, their treatment increased retinal thickness. They also posted only a marginal improvement in visual acuity of ~2.2 letters over baseline.
Molecular Partners/Allergan (now Actavis)	abicipar like DARPIn + anti-PDGF DARPIn	PDGF+VEGF-A	Pre-clinical	Intravitreal injection	Promising approach however similar to abicipar will have to differentiate itself from Regeneron's drugs. We understand there are some challenges in the ability to manufacture the DARPins.
Regeneron	REGN910-3	ANG2+VEGF-A	Phase 1	Intravitreal injection	Co-formulation of ANG2 antibody with Eylea. Trial initiated in 4Q14. Data from the trial expected towards the end of CY15.
Tyrogenex	X-82	PDGF+VEGF-A	Phase 2	Oral	The Phase II trial is enrolling wet AMD patients previously treated with Eylea. Given the route of administration, the drug will have systemic exposure and we are uncertain about potential commercial adoption by ophthalmologists.
Ohr Pharma	OHR-102	VEGF, PDGF, and basic fibroblast growth factor (bFGF)	Phase 2 AMD trial failed. Company looking at other eye indications such as retinal vein Occlusion	Topical (Eye drop formulation)	The focus of this product was to be a complementary product to Lucentis, so when taken together, it would reduce the frequency of Lucentis injections required by a patient. Its Phase 2 trial failed to meet its primary endpoint. The drug OHR-102 failed to meaningfully decrease the mean number of injections vs. the control arm which got placebo eye drops instead.

SOURCE: BELL POTTER SECURITIES, COMPANY DATA

Comparable deals in eye disease space

With only three anti-VEGF-A drugs used to treat wet AMD (one of which is off-label), the market for wet AMD is largely untapped and underserved. The multi-billion dollar market with relatively low competition, characterised by an unmet need for new wet AMD therapies that could improve visual acuity over current standard of care anti-VEGF-A therapies, ensures that pharma companies remain on the lookout for promising assets to license. Specifically we have observed that the industry is receptive to a combination approach with anti-VEGF-A therapy in wet AMD and sees multi-billion dollar potential in this approach.

Looking at some of the deals listed in the table below, the average deal size in the ophthalmology drug space is ~US\$500m (excluding the Molecular Partners/Allergan \$1.46bn deal in 2012 and the AGTC/Biogen deal in 2015). We include the Ophthotech/Novartis deal in the average given its direct relevance to Circadian. At this stage, in the absence of clinical data from OPT-302, we use the average deal size as a reasonable assumption for the dollar value CIR's OPT-302 may fetch.

We forecast that OPT-302 gets licensed in CY1H18 for a total deal package of US\$500m, including US\$55m in upfront and US\$15m in near term milestone payment. We also expect tiered double digit royalties on net sales to be part of the deal ranging from 15%-22%, should OPT-302 successfully reach the market. For conservatism sake, we model a flat rate of 18% for now.

Table 5 –Licensing deals in the ophthalmology space

Date	Company	Product	Indication	Stage at licensing	Licensee	Total deal value in USDm (upfront plus milestones)	Upfront (USDm)	Milestones (USDm)	Note
May-14	Ophthotech	Fovista (anti-PDGF) and potential fixed combination co-formulation of Fovista with NVS's anti-VEGF product	Wet age-related macular degeneration (AMD)	Phase 3	Novartis	1030	200	830	Ex US rights only. Includes \$130m in development milestones, \$300m in Ex-US approval milestones and up to \$400m in sales milestones. OPHT retained US rights. Deal included mid-30% royalty on net sales of Fovista standalone product and a royalty of approximately equal value on sales of co-formulated Fovista products. NVS to also develop a Fovista pre-filled syringe. OPHT retains option to obtain US rights to co-formulated product and pre-filled syringe. NVS and OPHT to cost share Fovista development outside the US. OPHT to fund and be responsible for ongoing Phase III's and US registration.
May-11	Molecular Partners	MP0112/abicipar (DARPin protein)	Various retinal indications including wet AMD	Phase 2	Allergan (now Actavis)	420	45	375	Global rights. Phase IIb costs to be shared, with Allergan responsible for Phase III and commercialization. Includes \$225m in development and regulatory milestones and \$150m in sales milestones. Deal also includes tiered double-digit royalties on net sales.
Oct-06	Regeneron	Eylea	Wet AMD, DME and other retinal diseases	Phase 2	Bayer	320	75	245	Ex US rights only. Includes \$110m in development and regulatory milestones and up to \$135m in sales milestones. Regeneron retained US rights. Bayer and Regeneron to share development costs and share profits equally from Ex-US sales.
Aug-12	Molecular Partners	2 agreements covering up to 4 compounds. One covers MP0260 (bispecific DARPin VEGF-A/PDGF-B inhibitor), second covers up to 3 DARPins	Wet AMD, various eye diseases	Preclinical (MP0260), second is discovery stage	Allergan (now Actavis)	1462.5	62.5	1400	Includes tiered royalties up into the low double-digits for future product sales. On first compound both companies will collaborate for proof of concept study and then Molecular Partners has option to co-fund further development for a significant step-up in royalties. On second agreement Allergan has option to license up to 3 compounds under the collaboration by paying an option exercise fee and will be responsible for all future development and commercialization costs.
Jan-14	Regeneron	Combination of PDGFR-beta antibody and Eylea (VEGF-A inhibitor) in single intra-vitreal injection	Wet AMD	Phase 1 ready	Bayer	65.5	25.5	40	Ex US rights only. Both companies will share global development costs. Bayer will share equally profits from Ex-US sales with Regeneron. Regeneron keeps US rights and 100% of profits from US sales. Milestones are option and regulatory approval related. Bayer will also be responsible for third party payments including any royalties on ex-US sales and development milestones due to third party.
May-14	Avalanche Biotechnologies	Up to 8 therapeutic targets including AVA-311 (gene therapy)	Various	Discovery with the exception of AVA-311 which was in preclinical stage	Regeneron	648	8	640	Option agreement. Includes tiered low- to mid-single-digit royalties on worldwide net sales of any collaboration product candidates. Milestones are \$80m each and are development and regulatory related. Avalanche has option for any 2 candidates to share up to 35% of global development costs and profits. Regeneron will bear all costs of development. Regeneron also has time-limited right of first refusal to license Avalanche's lead candidate AVA-101 (comprised of the AAV2 vector, which contains a gene encoding sFLT-1, a naturally occurring anti-VEGF protein).
Jul-15	Applied Genetic Technologies Corporation (AGTC)	5 candidates (gene therapy)	Various Ophthalmic diseases including two orphan eye diseases, and one discovery stage candidate for a non-ophthalmic indication	1 Phase 1, 1 preclinical, rest discovery	Biogen	1189	124	1065	Upfront payment includes \$30m equity investment. \$472.5m milestones linked to two lead programmes while \$592.5m milestones linked to other discovery stage programs. 2 lead programmes will bear royalties ranging from high-single-digit to mid-teen percentages and for discovery stage programs the royalty rate is slightly less at mid-single digits to low-teen percentages of net sales. AGTC retains the option to share development costs and profits, as well as the possibility to co-promote the second of these products to be approved in the US.
					Average	497	71		

SOURCE: COMPANY DATA AND BELL POTTER SECURITIES

Major Financial Assumptions

Revenues: The revenue driver in our model is Circadian's core asset OPT-302 for the indication of wet AMD. We assume that the asset gets licensed after completion of Phase 2B trials in CY1H18, with the partner assuming all future development, regulatory and marketing costs and paying upfront and milestone payments to Circadian and royalties on net sales, in return for exclusive worldwide rights to the drug.

Our revenue forecasts for Circadian are broken down into the following two categories:

- **Collaboration revenue:** This comprises of our estimated US\$500m of potential upfront and milestone payments receivable by Circadian from a potential licensee for OPT-302. Also included in this is potential royalties on net sales (BPe 18% royalty rate) from OPT-302 after its potential launch in the wet AMD market in FY22. We have used a patient-driven market model for wet AMD to estimate the sales trajectory of OPT-302.
- **R&D revenue:** This includes the R&D Tax incentive received by Circadian from the Australian Government and any grant revenue received by Circadian to assist in the development of its pipeline. We don't include any future grant revenue in our forecasts. We include R&D tax incentive in our forecasts only for the next two years during which Circadian will be running its Phase 1/2A and 2B trials for OPT-302.

Key assumptions used in market model to arrive at peak sales for OPT-302

We model US\$1.5bn peak worldwide sales (pre risk adjustment) for OPT-302 in wet AMD. Our forecasts are based on the following assumptions:

- There are ~1.3m wet AMD patients in the US and EU who are treated with an anti-VEGF-A therapy currently.
- We assume that moving forward the share of the three anti-VEGF-A drugs in the US remains steady, with off-label Avastin accounting for ~44% of treated patients and the brand share of the market at 56% (i.e. Lucentis and Eylea). We assume that Eylea has a slightly higher share of the market than Lucentis.
- For Europe, the market share dynamics are slightly different to US. We assume the branded share of the market is around 70% with Avastin having about 30% of the market. Between the two brands we assume that Eylea has about one-third of the branded market. We expect Eylea still has scope to gain market share. We expect steady market share in future with both Eylea and Lucentis splitting the branded market in half and Avastin's share dropping another couple of points.
- We assume that the 2 PDGF and OPT-302 add on therapies at peak are used in 37% of VEGF-A treated patients in the US and 34% of VEGF-A treated patients in EU.
- We assume that PDGF combination therapies (including Fovista) and OPT-302 at peak will have equal share of the Lucentis and Avastin treated patients who will receive add on therapy. However, we assume that for Eylea treated patients, PDGF therapy will have a slightly higher share than OPT-302 both in the US and EU. This is based on our assumption that Regeneron's co-formulation of anti-PDGF with Eylea (REGN2176-3) is also approved and available in the wet AMD market prior to OPT-302 launch.
- We expect that at Peak on a worldwide basis, OPT-302 is used in ~19% of Lucentis treated patients, 19% of Eylea treated patients and 14% of Avastin treated patients. Since price is a key factor in Avastin use, we assume add on therapy will be used relatively less in this group. This translates to OPT-302 being used in ~18% of VEGF-A treated patients in the US and ~16% of VEGF-A treated patients in Europe. Our market share assumptions are conservative and assume that at least two PDGF combination therapies are launched in the market ahead of OPT-302's launch. We also account for the fact that add on therapy is unlikely to be used for all VEGF-A treated patients.

- On average we assume each patient on OPT-302 will receive 5.5 injections of OPT-302 per year in line with current long term use of anti-VEGF-A therapies.
- We assume a gross price per vial of OPT-302 at launch of ~US\$1150 in the US, a 38%-43% discount to Eylea and Lucentis. We assume that Fovista from Ophthotech gets launched at ~US\$1500 in the US. At this stage given the absence of clinical data from OPT-302, our launch price for OPT-302 is also based on the assumption that Fovista having the first mover advantage will command a higher price (assuming OPT-302 has equivalent safety and efficacy to Fovista). We note that the price will ultimately be dictated by efficacy. So if OPT-302 ends up having better clinical data than Fovista, it is likely to command a higher price.
- We assume OPT-302 gets launched in the US in FY22 and in EU in FY23.

We risk-adjust our net sales numbers for OPT-302 as well as the upfront and milestone payments from a potential deal based on our assumed probability of success, which in turn is dependent on the clinical phase of its development.

We have used Bell Potter's current long term assumption for the AUD/USD cross rates to convert the USD collaboration revenue numbers to AUD in our model.

R&D costs: We assume that Circadian will spend ~\$9.5m between FY16-FY18 to complete a Phase 1/2A and Phase 2B trial for OPT-302 in wet AMD. We assume another \$3-4m gets spent on manufacturing and other pipeline during the period. We expect R&D costs to decline once OPT-302 gets licensed in 1H CY18.

G&A costs: We expect G&A costs to be relatively stable over the next few years.

Capex: We expect CIR's capex requirements to be minimal as seen historically. Currently on its balance sheet, CIR has property, plant and equipment worth \$0.1m which is a miniscule amount. Its current capex relates to mostly office equipment and leasehold improvements. Thus, we estimate annual capex costs to be ~\$20,000.

Funding Position: At the end of FY15 (year ended 30th June 2015), Circadian had \$18.4m in cash. Circadian has no debt on its books. The company has ~\$3.1m in receivables on its balance sheet which relates to estimated tax refund from the Australian government under the R&D Tax incentive scheme and is expected to be received in FY16. Circadian completed a \$17.4m capital raising in November 2014 (\$14m placement and \$3.4m rights issue). The capital raising was a significant event in the company's history as it not only strengthened CIR's balance sheet but also introduced new institutional specialist healthcare names onto the company's register. **As per our current forecasts, the funding provides cash runway through to the end of CY17.** Circadian's current cash position allows it to fund the ongoing Phase 1/2A trial, as well as planned Phase 2B trial for OPT-302 in wet AMD. We assume cash injection from a licensing deal in CY1H18, should take care of funding requirements beyond 2017.

Circadian's Intellectual Property: Circadian has granted patents covering the composition of matter of soluble VEGFR-3 proteins family including OPT-302 in US, EU, Japan, Canada and Australia. The US patent expires in 2026 while the other markets have an expiry date of 2022. CIR also has a specific composition of matter patent application covering OPT-302 pending, which if granted will extend the patent life of OPT-302 to 2034. Circadian also has a US granted patent covering the use of VEGFR-3 to inhibit blood vessels in diseases characterised by the expression of VEGFR-3 which expire in 2023. We note that OPT-302 is likely to be eligible for further patent term extensions and additional data exclusivity in various jurisdictions by virtue of being a biologic. For example in the US, biologics are entitled to 12 years of data exclusivity. Also, compared to small molecules, being a biological product, the formulation of OPT-302 is likely to be more difficult to replicate and also require more exhaustive bioequivalence trials. This is why biologics tend to stave off generic competition for a much longer time even after their patents expire.

CIR's cash balance of \$18.4m provides cash runway to end of CY17

OPT-302 is likely to have patent protection at least out to 2034

Clinical Advisory Board and advisors

Circadian has established a world class Clinical Advisory Board (CAB) comprised of internationally recognised and experienced Key Opinion Leaders (KOL's) in the Field of Ophthalmology. Circadian's CAB represents a group of eminent physicians who have extensive experience in the development of emerging therapeutics for wet AMD including Ophthotech's Fovista and FDA approved anti-VEGF-A therapeutics for wet AMD, including Pfizer/Valeant's Macugen, Bayer/Regeneron's Eylea and Roche/Novartis' Lucentis.

The CAB provides key scientific, clinical and regulatory strategic guidance for the OPT-302 development program. They also provide valuable insights into ophthalmic drug development and commercialisation strategies.

As Circadian focuses on clinical development, partnership discussions, regulatory approvals and ultimate commercialization of OPT-302, the breadth, credentials, experience and professional recognition represented on their CAB will be highly important.

We believe that Circadian will look to partner its OPT-302 drug prior to Phase 3 trials. A potential licensee is likely to be a pharma company based in the US or Europe. Having the support of the KOL's in the field who are likely to be well known to the US and EU companies, could very well be the tipping point in favour of Circadian. Hence, we believe the quality of Circadian's CAB is of high significance.

In our view, CIR's ability to attract these eminent KOL's to be part of its CAB, imparts more credibility to the story, validates its technology and is a testament to the potential of OPT-302 to fulfil the unmet need of improved visual acuity in the wet AMD market. Circadian's Clinical Advisory Board is below.

Table 6 – Circadian's Clinical Advisory Board is World Class

CAB Member	Experience
Pravin Dugel, MD	Dr Dugel serves as Managing Partner of Retinal Consultants of Arizona and Founding Member of the Spectra Eye Institute. He is also Clinical Professor, Department of Ophthalmology, Keck School of Medicine, University of Southern California (USC). Dr Dugel is internationally recognised as a major clinical researcher having served as Principal Investigator for over 50 multicenter clinical trials for emerging and subsequently FDA approved therapies for wet AMD, including Fovista®, Lucentis® and Eylea® and was recently named "one of the best 35 ophthalmologists in the USA" by the Becker Institute. He has authored more than 200 papers, 35 book chapters and has been invited to lecture at prestigious meetings, visiting professorships and universities worldwide. He is on the Editorial Board of several major journals. His research and educational contributions earned him the prestigious Senior Honor Award from the American Academy of Ophthalmology (AAO). He is on the Board of Directors of the American Society of Retina Specialists (ASRS), Chairman of the ASRS Research and Therapeutics Committee and Chairman of the AAO Media Relations Committee. Internationally, he is on the Board of Directors of the Asia Pacific Vitreoretinal Society. Dr Dugel has received numerous awards including amongst others, the Heed Foundation Fellowship Award, The Ronald G. Michels Surgical Fellowship Award, AAO Senior Honor Award, ASRS Honor Award and the AAO Secretariat Award.
Mark Gillies, MBBS, PhD	Professor Mark Gillies is a retinal clinician with a 25 year history of laboratory and clinical research in retinal disease. He was the first Australian ophthalmologist to be awarded a PhD, which he received for his work on diabetic retinopathy at the Walter and Eliza Hall Institute. Having trained in ophthalmology at Prince of Wales Hospital he moved to the University of Sydney's Save Sight Institute, after a period of sabbatical study in Boston and London, where he is currently a Sydney Medical School Foundation Fellow. Directing the Macular Research Group at the University of Sydney, Mark Gillies is a clinician-scientist with an interest in developing improved treatments for macular disease, particularly macular oedema, and degenerative macular conditions. Professor Gillies is the Scientific Manager of the MacTel Project, an international project to identify a cure for Macular Telangiectasia Type 2. He has been a scientific advisor to the Macular Photocoagulation Study group, the world's leading investigator initiated study group for retinal diseases, and the United States' National Eye Institute-funded Diabetic Retinopathy Collaborative Research Network. Dr Gillies serves as the Vice Chairman of the Board of the Ophthalmic Research Institute of Australia and has also served on the Board of the Fred Hollows Foundation since its inception in 1992. In addition, he is on advisory boards and has received research support from Bayer, Novartis and Allergan. He has more than 140 publications, mostly concerned with the treatment of macular diseases and retinal cell biology.
Peter Campochiaro, MD	Dr Campochiaro is the George S. and Dolores Dor Eccles Professor of Ophthalmology and Neuroscience at the John Hopkins Wilmer Eye Institute. He was trained at the University of Notre Dame, Johns Hopkins School of Medicine, the University of Virginia, and Wilmer, joining the Wilmer Faculty in 1991. Dr Campochiaro is a clinician-scientist with an interest in understanding the molecular pathophysiology of ocular neovascularization and vascular leakage with the goal of developing new treatments for retinal diseases. His laboratory research group helped to demonstrate the importance of the vascular endothelial growth factor (VEGF) pathway in retinal and choroidal vascular diseases and as a clinician he has had significant experience in many of the clinical studies evaluating anti-VEGF-A therapies such as Lucentis® (Genentech/Roche) and Eylea® (Regeneron/Bayer). As a respected and prominent clinical researcher, Dr Campochiaro serves as a member of the Scientific Advisory Boards of Asclepix Therapeutics, CoMentis, Inc., Eyegate Pharmaceuticals, Inc, Potentia Pharmaceuticals and RXi Pharmaceuticals. Dr Campochiaro has more than 300 articles published in peer reviewed medical journals.
Kameron Lashkari, MD	Dr. Lashkari currently holds several academic positions including Clinical Assistant Scientist, Schepens Eye Research Institute and Clinical Instructor of Ophthalmology at Harvard Medical School. He is Assistant in Ophthalmology at the Massachusetts Eye and Ear Infirmary. Dr Lashkari received his medical degree from New York Medical College and is board certified in the fields of ophthalmology and internal medicine. He completed his Internal Medicine residency at St. Vincent's Hospital and Medical Center in New York City, and his Ophthalmology residency at the University of Missouri Eye Foundation of Kansas City. Dr Lashkari completed medical and surgical fellowships in vitreoretinal disease at Massachusetts Eye and Ear Infirmary, Harvard Medical School, and Schepens Retina Associates. In addition, he has completed a research fellowship at Schepens Eye Research Institute.

SOURCE: COMPANY DATA

Circadian's key advisors in ophthalmology also include Dr Emmett Cunningham (Chairman of the Ophthalmology Innovation Summit, San Francisco), Dr Denis O'Shaughnessy (formerly Senior Vice President of Clinical Affairs at Oraya Therapeutics, clinical consultant to Xcovery Vision and founding member of Eyetech Pharmaceuticals), Dr David Worsley (retinal ophthalmologist, Hamilton Eye Clinic, New Zealand) and Dr Robert Finger (retinal ophthalmologist, Royal Victorian Eye and Ear Hospital and Centre for Eye Research Australia).

Board and Management

Circadian's Board of Directors is below.

Table 7 – Circadian's Board of Directors have a broad range of skills and experience			
Directors	Position	Year Appointed	Experience
Megan Baldwin	Managing Director & CEO	2014	Dr Baldwin brings over 19 years of experience focussing on angiogenesis and therapeutic strategies for cancer and ophthalmic indications. She joined Circadian in 2008 and since then has held various positions, including Head of Preclinical R&D and CEO of Opthea Pty Ltd, the 100% owned subsidiary of Circadian, developing OPT-302 (formerly VGX-300) for the treatment of wet age-related macular degeneration. Prior to joining Circadian, she was employed at Genentech (now Roche), the world leader in the field of angiogenesis-based therapies for cancer and other diseases. Her experience included several years as a researcher in the group of leading angiogenesis expert Napoleone Ferrara, before moving to Genentech's commercial division and having responsibility for corporate competitive intelligence activities. In these roles, she developed extensive commercial and scientific knowledge in the field of anti-angiogenic and oncology drug development. She holds a PhD in Medicine from the University of Melbourne, having conducted her doctoral studies at the Ludwig Institute for Cancer Research and is a member of the Australian Institute of Company Directors.
Dominique Fisher	Chairman & Non-Executive Director	2005	Ms Fisher is also a member of the Company's Audit and Risk and Remuneration Committees. She is a non-executive director of Australia Post, Principal and Executive Director of EC Strategies Pty Ltd and the executive chairman of CareerLounge Pty Ltd. Her past appointments have included a non-executive director of Pacific Brands Limited and membership of its Audit and Risk Committee, chairman of Sky Technologies Pty Ltd, Councillor of the Australia Council of the Arts, and chairman of its Dance Board, Insurance Australia Group Limited (IAG), member of the Prostate Cancer Foundation Victoria, NRMA, the Malthouse Theatre, Sydney Opera House and member of the ICT Advisory Board, advising the Federal Government on key issues affecting the development of the information technology and communications sector.
Tina McMeckan	Non-Executive Director	2008	Ms McMeckan is also the Chairman of the Company's Audit and Risk Committee and a member of the Remuneration Committee. Her specific skills are in the commercialisation of science and technology and the energy sector. She is presently a director of CRC for Spatial Information, Ausnet Services Limited, and the Global Carbon Capture and Storage Institute and was the Chairman of Centre for Eye Research Australia until November 2012 and a director of Metlink Pty Ltd until April 2012. She is a past member of the Funds Management Committee of the AusIndustry Research and Development Board and has held senior investment management positions with the Australian Industry Development Corporation and Amrad Corporation Ltd (acquired by CSL Limited), focusing on capital raisings for innovation-based ventures. She also has extensive board expertise in public and private utility infrastructure, including power production, networks and retailing business in the gas and electricity industries. She was formerly the Chairman of NanoVentures Australia Ltd and a member of the National Board of Norton Rose law firm. Her other appointments as a director have included United Energy, Snowy Hydro Trading, the Westar and Kinetik Energy Group, Victorian Power Exchange, Vision Cooperative Research Centre, Solaris Power and the formerly listed company Alinta Limited (October 2003 to August 2007).
Russell Howard	Non-Executive Director	2013	Dr Howard has acted as a special advisor to the board of directors since 2012. He has extensive experience in the life sciences and biotechnology sectors. Dr Howard is executive chairman at Neulclone, a Sydney company developing biosimilar monoclonal antibody drugs. He is also the founder and non-executive chairman of Oakbio, a biotechnology company based in California, developing breakthrough sustainable microbe-based technologies that convert CO ₂ in waste gas into valuable chemical products. Previously, Dr Howard was Founder and CEO of Maxygen, President & Scientific Director at Affymax and he also previously served on advisory panels for WHO and USAID. He is presently also on the Board of Australian biotech company Prima Biomed.

SOURCE: COMPANY DATA

Apart from the CEO Megan Baldwin (as mentioned above), the other key members of Circadian's leadership team are:

Chief Financial Officer & Company Secretary: Mike Tonroe (Since 2014)

CFO & CS Mike Tonroe has previously held CFO and senior executive and general management positions in a number of companies in Australia, UK, the US and Canada. He is a Chartered Accountant. He is also the Company Secretary for Syngene Limited, Vegenics Pty Ltd and all other Circadian subsidiary companies.

Head of Clinical Development: Ian Leitch (Since 2011)

Mr. Leitch has over 15 years of research and management experience from drug discovery through clinical development in biotechnology/pharmaceutical companies. For the 5 years prior to joining Circadian, he was a member of the Medical Sciences group at Amgen Inc, involved in the development of novel therapeutics in Amgen's oncology pipeline. In his role as Senior Manager in the Early Development Oncology Therapeutic Area, he had responsibility for the oversight, design, management and execution of Phase 1-2 clinical studies in oncology. Prior to joining Amgen, he spent eight years at the ophthalmology drug development company Miravant Medical Technologies in US, where he held several senior positions. He previously held the position of NHMRC Senior Research Officer at the Uni of Newcastle, and was based at the John Hunter Hospital in Australia.

Head of CMC (chemistry, manufacturing and controls) Development: Mike Gerometta (Since 2008)

Mr. Gerometta is principally responsible for cGMP manufacturing and management of the toxicology program. He has over 20 years of experience in the Australian biotechnology industry, most recently as COO of Q-Gen, QIMR's translational research, manufacturing arm. Previously he spent 19 years at Agen Biomedical, where he held several senior positions including as Research and Product Development Director. He was awarded his PhD in biotechnology from the Queensland University of Technology and has a degree in chemistry from the University of Technology in Sydney.

Key Shareholders

Substantial Shareholders

The combined holdings of the Top 3 shareholders of Circadian represent ~35.4%. The largest shareholders of Circadian are shown in the table below:

Figure 9 – Substantial Shareholders in Circadian

Investor	No of shares held	% current holding
BVF Partners LP	26,998,691	17.98%
Baker Brothers Life Sciences LP	13,537,758	9.01%
Packer and Co Limited	12,700,488	8.46%

SOURCE: COMPANY DATA

Top 20 Shareholders

The Top 20 shareholders in Circadian are shown in the Figure below.

Figure 10 - Top 20 Shareholders in Circadian (as of 12th August, 2015)

Top 20 shareholders as of 12th August 2015	No. of ordinary shares	% holding
National Nominees Limited	23,087,445	15.4%
Citicorp Nominees Pty Limited	16,467,484	11.0%
HSBC Custody Nominees (Australia) Limited-GSCO ECA	13,537,758	9.0%
HSBC Custody Nominees (Australia) Limited	13,197,020	8.8%
BNP Paribas Noms Pty Ltd <Drp>	12,702,988	8.5%
J P Morgan Nominees Australia Limited	7,894,306	5.3%
Armada Trading Pty Limited	5,714,286	3.8%
Jagen Pty Ltd	5,714,286	3.8%
Ludwig Institute For Cancer Research Ltd	3,122,090	2.1%
UBS Nominees Pty Ltd	2,500,000	1.7%
HSBC Custody Nominees (Australia) Limited - A/C 3	2,000,000	1.3%
Capital Macquarie Pty Limited	1,928,304	1.3%
Megan Baldwin	1,533,674	1.0%
Dr Choon-Joo Kho	1,200,000	0.8%
Octavian Services Pty Ltd	1,200,000	0.8%
4 Eyes Limited <Worsley Family A/C>	1,165,890	0.8%
Chemical Trustee Limited	1,158,108	0.8%
CS Fourth Nominees Pty Ltd	1,037,059	0.7%
Capita Trustees Limited <Mk Pension Plan-473278 A/C>	946,462	0.6%
Traders Macquarie Pty Limited	907,161	0.6%
Total Top 20 investors holding	117,014,321	77.9%
Total Other Investors	33,175,982	22.1%
Total Shares on Issue	150,190,303	100.0%

SOURCE: COMPANY DATA

Escrow and Free Float

A portion of the shares held by the Chairman and the CEO are subject to voluntary escrow. These holdings total 2.1m shares or 1.4% of issued capital. We therefore estimate the free float of the company to be 98.6%. The voluntary escrow is in place till 1st July 2016.

The details of the shares under escrow in Circadian are shown in the Figure below.

Figure 11 – Shares under Voluntary Escrow

Directors	No. of ordinary shares under escrow	% holding	Position
Dominique Fisher	600,000	0.40%	Chairman & Non-Executive Director
Megan Baldwin	1,500,000	1.00%	CEO & Managing Director
Shares under escrow	2,100,000	1.40%	
Free Float		98.60%	

SOURCE: COMPANY DATA

Risks

The key risks specific to Circadian include, but are not limited to, the following:

- **Clinical risk:** There is a risk that CIR's clinical trials for OPT-302 fail to reach their endpoints, which would in turn impact its partnering prospects.
- **Reliance on partnerships in our model:** Our valuation is underpinned by CIR's ability to ultimately attract a valuable partnering deal for its OPT-302 asset. Failure to attract licensees for this drug candidate or to negotiate attractive deal terms as we have postulated will severely impact our forecasts.
- **Reliance on one drug to drive value:** The revenue driver in our model is OPT-302 for the indication wet AMD. While there are other non-core assets which could drive additional value in future, we believe CIR is vulnerable to the success/failure of clinical trials of OPT-302, impacting the sentiment around the whole company.
- **Regulatory risk:** Successful commercialisation of CIR's OPT-302 is ultimately dependent on getting approval from the regulatory authorities to commercially launch the product. Failure to satisfy regulatory requirements could mean that the product will fail to reach the market.
- **Commercial risk:** There is no guarantee that mid-late stage OPT-302 clinical trial results, even if they hit the endpoints of the studies, will be viewed as clinically meaningful by clinicians and other stakeholders. Even if the drug does get approved on successful pivotal studies, commercial adoption might still be hampered by the cost of the combination (i.e. OPT-302 plus anti-VEGF-A agent), or the dosing frequency used in pivotal studies, or clinicians finding two injections as cumbersome or the competition in the wet AMD market having much larger impact than we have postulated.
- **Funding risk:** Delays in partnering of OPT-302 and subsequently in receipt of upfront/milestone payments from the licensee may impact CIR's funding position in the long term. Although CIR has a high cash balance currently which should provide cash runway to end CY17, the company may need to raise additional capital if it wishes to self-fund a Phase 3 trial for OPT-302. There is no guarantee that CIR will be able to secure additional financing if and when required.

CIR had ~A\$18.4m cash at the end of FY15

Table 8 - Financial summary

Circadian Technologies (CIR)						Share price (A\$)	\$0.200				
As at 10 September 2015						Market cap (A\$m)	30.0				
Profit and Loss											
Y/e June 30 (A\$m)	2014A	2015A	2016E	2017E	2018E						
Revenue*	3.7	3.3	1.5	3.4	25.4						
EBITDA**	-3.9	-6.0	-5.9	-8.6	18.4						
Depreciation & Amortisation	0.0	0.0	0.0	0.0	0.0						
EBIT	-4.0	-6.1	-5.9	-8.6	18.3						
Net interest & Other Income/(Expense)	0.0	0.7	0.5	0.3	0.5						
Pre-tax profit	-4.0	-5.4	-5.4	-8.3	18.9						
Tax	0.0	0.0	0.0	0.0	5.7						
NPAT (adjusted) before allocation to Minority Interests	-4.0	-5.4	-5.4	-8.3	13.2						
Less minority interests	0.0	-0.1	-0.1	-0.1	0.2						
Net profit (loss) to shareholders	-4.0	-5.3	-5.4	-8.2	13.0						
One off items	0.0	0.0	0.0	0.0	0.0						
Reported Net profit (loss) to shareholders	-4.0	-5.3	-5.4	-8.2	13.0						
* Includes R&D tax incentive. FY18 revenue includes risk adjusted upfront payment from licensing deal for OPT-302. EBITDA excludes other non-operating income/expense.											
Cashflow											
Y/e June 30 (A\$m)	2014A	2015A	2016E	2017E	2018E						
Reported NPAT plus minority interests	-4.0	-5.4	-5.4	-8.3	13.2						
Non-cash items	-2.5	-2.5	-1.0	-2.8	0.6						
Net change in Working capital	2.3	2.8	3.0	1.7	3.4						
Operating cashflow	-4.2	-5.0	-3.4	-9.5	17.2						
Capex	-0.1	0.0	0.0	0.0	0.0						
Investments	0.5	0.0	0.0	0.0	0.0						
Other investing cash flow	0.0	0.0	0.0	0.0	0.0						
Investing cashflow	0.3	0.0	0.0	0.0	0.0						
Change in borrowings	0.0	0.0	0.0	0.0	0.0						
Equity issued	0.0	16.1	0.0	0.0	6.7						
Dividends paid	0.0	0.0	0.0	0.0	0.0						
Other financing cash flow	0.0	0.0	0.0	0.0	0.0						
Financing cashflow	0.0	16.1	0.0	0.0	6.7						
Net change in cash	-3.8	11.1	-3.5	-9.5	23.9						
Cash at end of period*	7.2	18.4	15.0	5.4	29.4						
* Includes effect of exchange rate fluctuations on cash balance											
Free cash flow	-4.3	-5.0	-3.5	-9.5	17.2						
Balance sheet											
Y/e June 30 (A\$m)	2014A	2015A	2016E	2017E	2018E						
Cash	7.2	18.4	15.0	5.4	29.4						
Current receivables	2.7	3.3	1.7	3.6	0.2						
Inventories	0.0	0.0	0.0	0.0	0.0						
Other current assets	0.1	0.1	0.1	0.1	0.1						
Current assets	10.0	21.9	16.8	9.2	29.7						
PPE	0.1	0.1	0.1	0.1	0.0						
Non-current receivables	0.0	0.0	0.0	0.0	0.0						
Intangible assets	0.0	0.0	0.0	0.0	0.0						
Other non-current assets	2.3	2.0	2.0	2.0	2.0						
Non-current assets	2.5	2.2	2.1	2.1	2.1						
Total assets	12.5	24.1	19.0	11.3	31.8						
Payables	1.6	2.0	1.8	1.9	1.8						
Debt	0.0	0.0	0.0	0.0	0.0						
Provisions	0.2	0.3	0.4	0.4	0.5						
Other liabilities	0.1	0.1	0.1	0.1	0.1						
Total liabilities	2.0	2.4	2.2	2.4	2.4						
Shareholders' equity	9.5	20.9	16.0	8.3	28.6						
Minorities	0.9	0.8	0.7	0.6	0.8						
Total shareholders funds	10.5	21.7	16.7	8.9	29.4						
Total funds employed	12.5	24.1	19.0	11.3	31.8						
W/A Diluted shares on issue	48.6	109.1	149.6	150.7	170.6						
SOURCE: BELL POTTER SECURITIES ESTIMATES											
Valuation data											
Y/e June 30	2014A	2015A	2016E	2017E	2018E						
Adjusted Net profit (A\$m)	-4.0	-5.3	-5.4	-8.2	13.0						
EPS (c)	-8.22	-4.87	-3.58	-5.44	7.61						
EPS growth (%)	N/A	N/A	N/A	N/A	NM						
P/E ratio (x)	N/A	N/A	N/A	N/A	2.6						
CFPS (c)	-8.6	-4.6	-2.3	-6.3	10.1						
Price/CF (x)	-2.3	-4.3	-8.7	-3.2	2.0						
DPS (c)	0.0	0.0	0.0	0.0	0.0						
Yield (%)	0.0%	0.0%	0.0%	0.0%	0.0%						
Franking (%)	N/A	N/A	N/A	N/A	N/A						
EV/EBITDA	-3.0	-1.9	-2.0	-1.3	0.6						
EV/EBIT	-2.9	-1.9	-2.0	-1.3	0.6						
Share price now (A\$)						\$0.200					
Valuation (A\$):						\$0.38					
Premium (discount) to price						90.0%					
Recommendation:						Buy					
Risk Rating						Speculative					
Profitability ratios											
Y/e June 30	2014A	2015A	2016E	2017E	2018E						
EBITDA/revenue (%)	N/A	N/A	N/A	N/A	72.4%						
EBIT/revenue (%)	N/A	N/A	N/A	N/A	72.2%						
Return on assets (%)	-32.1%	-22.1%	-28.2%	-72.5%	40.8%						
Return on equity (%)	-41.8%	-25.8%	-34.0%	-100.0%	46.2%						
Return on funds empl'd (%)	-38.1%	-24.5%	-31.9%	-91.8%	44.1%						
Dividend cover (x)	N/A	N/A	N/A	N/A	N/A						
Effective tax rate (%)	0.0%	0.0%	0.0%	0.0%	30.0%						
Liquidity and leverage ratios											
Y/e June 30	2014A	2015A	2016E	2017E	2018E						
Net cash (debt) (A\$m)	7.2	18.4	15.0	5.4	29.4						
Net debt/equity (%)	N/A	N/A	N/A	N/A	N/A						
Net interest cover (x)	N/A	N/A	N/A	N/A	N/A						
Current ratio (x)	5.7	9.8	8.0	4.1	13.1						
Interims											
Y/e June 30 (A\$m)	2H14A	1H15A	2H15A	1H16E	2H16E						
Revenue	1.5	1.5	1.8	0.8	0.8						
EBITDA	-2.1	-3.3	-2.8	-2.7	-3.2						
Depreciation & Amortisation	0.0	0.0	0.0	0.0	0.0						
EBIT	-2.1	-3.3	-2.8	-2.7	-3.3						
Net interest & Other Expense	-0.3	0.3	0.4	0.2	0.3						
Pre-tax profit	-2.4	-3.0	-2.4	-2.5	-2.9						
Tax	0.0	0.0	0.0	0.0	0.0						
Adjusted Net Profit	-2.4	-3.0	-2.4	-2.5	-2.9						
Less minority interests	0.0	-0.1	0.0	0.0	0.0						
Net profit to shareholders	-2.4	-2.9	-2.4	-2.5	-2.9						

Recommendation structure

Buy: Expect >15% total return on a 12 month view. For stocks regarded as 'Speculative' a return of >30% is expected.

Hold: Expect total return between -5% and 15% on a 12 month view

Sell: Expect <-5% total return on a 12 month view

Speculative Investments are either start-up enterprises with nil or only prospective operations or recently commenced operations with only forecast cash flows, or companies that have commenced operations or have been in operation for some time but have only forecast cash flows and/or a stressed balance sheet.

Such investments may carry an exceptionally high level of capital risk and volatility of returns.

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Disclosure: Bell Potter Securities acted as lead manager for a \$14m capital raising and as an underwriter for a \$3.4m rights issue in November 2014 and received fees for that service. Bell Potter Securities holds 1 million Circadian options exercisable at 26.25 cents by 13th January 2018.

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The stocks of biotechnology companies without strong revenue streams from product sales or ongoing service revenue should always be regarded as speculative in character. Since most biotechnology companies fit this description, the speculative designation also applies to the entire sector. The fact that the intellectual property base of a typical biotechnology company lies in science not generally regarded as accessible to the layman adds further to the riskiness with which biotechnology investments ought to be regarded. **Stocks with 'Speculative' designation are prone to high volatility in share price movements.** Clinical and regulatory risks are inherent in biotechnology stocks. Biotechnology developers usually seek US FDA approval for their technology which is a long and arduous three phase process to prove the safety, effectiveness and appropriate application or use of the developed drug and even after approval a drug can be the subject of an FDA investigation of subsequently discovered possible links between the drug and other diseases not previously diagnosed. Furthermore, the Australian exchange listed biotechnology sector is subject to influence by the global biotechnology sector, particularly that in the USA. Consequently, Australian exchange listed biotechnology stocks can experience sharp movements, both upwards and downwards, in both valuations and share prices, as a result of a re-rating of the sector both globally and in the USA, in particular. Investors are advised to be cognisant of these risks before buying such a stock including **Circadian Technologies**. For a list of risks specific to Circadian please refer to Page 29 of this note.

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