30 April 2024
ASX and NASDAQ

Quarterly Activity Report

Q3 FY24

Highlights

- Completion of enrolment in first trial of sozinibercept's Phase 3 pivotal program ("COAST")
- Appointments of SVP Clinical Development and SVP Regulatory Affairs
- Appointment of Dr. Arshad Khanani, MD, MA, FASRS as Chief Medical Advisor
- On track to complete enrolment of the second Phase 3 pivotal trial ("ShORe") in 2Q of CY2024
- Expected topline data from both phase 3 trials of Sozinibercept in mid-calendar year 2025

Opthea Limited (ASX: OPT, NASDAQ:OPT) ("Opthea" or "the Company"), has today released its Quarterly Activity Report and Appendix 4C for the three-month period ended 31 March 2024 ("Q3 FY24").

Opthea is a clinical-stage biopharmaceutical company developing novel therapies to treat highly prevalent and progressive retinal diseases, including wet age-related macular degeneration (wet AMD) and diabetic macular edema (DME).

Opthea's lead product candidate, sozinibercept, is being evaluated in two pivotal Phase 3 clinical trials (COAST and ShORe) for use in combination with standard-of-care anti-VEGF-A monotherapy to improve overall efficacy and deliver superior vision gains compared to standard-of-care anti-VEGF-A agents.

Sozinibercept has the potential to be the first new drug for wet AMD in more than 15 years to deliver superior visual gains when administered in combination with any anti-VEGF-A therapy for the treatment of wet AMD versus standard of care.

Dr. Fred Guerard, Chief Executive Officer of Opthea Limited, commented, "We are extremely pleased with the continued progress with sozinibercept and its potential for future clinical, regulatory and commercial success. Both global pivotal trials in wet AMD, with COAST fully enrolled and ShORe now 98% enrolled, aim at confirming the superior visual outcomes when used in combination with standard of care observed in Opthea's Phase 2b trial."

"We continue to build the Opthea team," Dr. Guerard added," and I am proud of the dedication and commitment to improving the lives of wAMD patients everyone at Opthea demonstrates."

ABN: 32 006 340 567

Lead drug sozinibercept
Opthea's lead candidate sozinibercept (OPT-302) is a first-in-class vascular endothelial growth factor (VEGF)-C/D inhibitor being developed as a combination treatment with VEGF-A inhibitors for the treatment of wet age-related macular degeneration and other retinal diseases. Wet AMD is a progressive, chronic disease of the retina and in developed nations is the leading cause of visual impairment in people over the age of 50 years.

Sozinibercept has the potential to be the first novel drug for wet AMD in more than 15 years to improve vision in wAMD patients when administered in combination with any anti-VEGF-A therapy relative to standard of care treatment.

Sozinibercept is a soluble form of vascular endothelial growth factor receptor 3 (VEGFR-3) expressed as an immunoglobulin G1 (IgG1) Fc-fusion protein. It binds and neutralizes the activity of VEGF-C and VEGF-D on their endogenous receptors, VEGFR-2 and VEGFR-3. Research indicates that targeted inhibition of VEGF-C and VEGF-D can prevent blood vessel growth and vascular leakage, which contribute to the pathophysiology of retinal diseases including wet AMD.

It is being evaluated in two pivotal Phase 3 clinical trials investigating sozinibercept in combination with VEGF-A therapies, the current standard-of-care, for the treatment of wet AMD. This strategy is intended to maximize the commercial opportunity for sozinibercept by improving overall efficacy and achieving superior vision gains over those demonstrated by anti-VEGF-A treatment alone. Sozinibercept has received Fast Track Designation from the U.S. FDA for the treatment of wet AMD.

The pivotal Phase 3 program is based on positive results from the Phase 2b trial of sozinibercept, administered in combination with standard of care, LUCENTIS® (ranibizumab), for the treatment of wet AMD. The trial, published in *Ophthalmology*, met the pre-specified primary efficacy endpoint of a statistically superior gain in visual acuity at 24 weeks, compared to ranibizumab alone. In addition, secondary outcomes were positive for the combination therapy with sozinibercept, including more participants with gains in vision of 10 or more letters and improved anatomy, with a reduction in swelling and vascular leakage, with a favorable safety profile.

Wet AMD
Wet AMD is associated with blood vessel dysfunction and proliferation in the macula, a region of the retina which is needed for sharp, central vision. New blood vessels break through layers of the retinal tissue, leaking fluid, lipids and blood, leading to fibrous scarring and loss of vision. Vision loss associated with wet AMD can be rapid and is generally severe, impacting patient independence and contributing to significant healthcare and economic costs worldwide.

Inhibitors of the VEGF family and wet AMD
Although the underlying cause and biology of wet AMD is complex, inhibition of vascular endothelial growth factor A, or VEGF-A, has been shown to play an important role in the growth and leakage of vessels associated with the disease, and inhibitors of VEGF-A are now standard of care treatments for wet AMD.

VEGF-A is a member of the VEGF family of proteins. It plays an important role in regulating the growth of abnormal new blood vessels and choroidal neovascularization in wet AMD. Opthea is investigating a first-in-class agent that targets VEGF-C and VEGF-D, additional ligand members of the VEGF family that are mediators of blood vessel growth and vascular leakage and are implicated in the progression of retinal diseases. VEGF-C and VEGF-D function independent of, but in parallel with, VEGF-A to drive these biological processes. In addition, suppression of VEGF-A increases VEGF-C and VEGF-D levels

and may contribute to suboptimal responses to anti-VEGF-A monotherapy.

By combining administration of sozinibercept with a VEGF-A inhibitor, broader blockade of the VEGF receptor-1, 2 and 3 signalling pathways that contribute to the pathophysiology of retinal diseases, can be achieved, with the potential to further reduce retinal swelling and improve visual acuity in patients. Furthermore, sozinibercept in combination with VEGF-A inhibitors, may result in more durable clinical responses.

Leadership Team

Opthea expanded its leadership team by appointing Dr. Arshad M Khanani as Chief Medical Advisor as well as strengthened the team with key clinical and regulatory appointments of Dr. Julie Clark, MD, MS as Senior Vice President of Clinical Development and Dr. Fang Li Ph. D RAC as Senior Vice President of Regulatory Affairs.

An internationally recognized retina specialist and clinical scientist, Dr. Khanani is a Managing Partner, Director of Clinical Research, and Director of Fellowship at Sierra Eye Associates, and Clinical Associate Professor at the University of Nevada, Reno School of Medicine. Over a decade ago, he established the clinical research department at Sierra Eye Associates, which has since evolved into one of the foremost clinical research sites nationwide. With a wealth of experience, he has assumed the role of principal investigator for more than 120 clinical trials, consistently ranking as a top enroller in the United State across multiple Phase 1 to Phase 3 trials.

With more than 15 years of experience in ophthalmology medical and clinical development, Dr. Clark brings expertise in both early and late-stage programs, regulatory submissions, and approvals. Her contributions include substantial support for the approval and launches of retinal therapies such as EYLEA®, JETREA® and BEOVU®. In Dr. Clark's most recent position as Vice President Clinical Development at IVERIC bio, Inc., An Astellas Company, she oversaw the development program leading to the August 2023 U.S. Food and Drug Administration (FDA) approval of IZERVAY™.

Dr. Li brings over 30 years of expertise in drug development and more than 20 years in regulatory affairs experience. Her experience spans various domains including small molecules, biologics, gene therapy, over-the-counter products, in-vitro diagnostic products and medical devices, with a specific focus on ophthalmology. She has held key roles at prominent ophthalmology companies such as Novartis AG, Alcon Inc., and Bausch + Lomb Corporation. Throughout her career, Dr. Li has played a pivotal role in leading numerous FDA drug approvals, including ophthalmology products JETREA®, LOTEMAX® Ointment, SYSTANE® COMPLETE.

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Third Quarter Financial Performance & Cash Flow

Opthea's cash balance at 31 March 2024 was US$101.6m, down from US$157.1m in the prior quarter ending 31 December 2023, primarily reflecting the continued spend on completing the two global, pivotal Phase 3 clinical trials.

Cash receipts for the quarter were US$0.7m, which is down 30% from the US$1.0m in the previous quarter. This decrease is a consequence of the varying interest on cash holdings. The net operating cash outflow for the period was US$51.6m. The prior period net operating cash outflow was US$40.6m.

Research and development cash costs for the quarter were US$42.7m, 6% above the previous quarter (Q2 FY24: US$40.1m). Administration cash costs in Q3 FY24 were US$5.1m and were slightly up from previous quarter (Q2 FY24: US$4.8m). Staff cash costs of US$3.9m were up 72% on the previous quarter of US$2.3m. These increases were in line with expectations with the additions of new staff in the quarter.

Use of Funds from Any Future Capital Raise

We intend to use the net proceeds from any future offering or capital raise to advance clinical development and Chemistry, Manufacturing, and Controls (CMC) activities of sozinibercept for wet AMD, through the reporting of topline data from two pivotal Phase 3 clinical trials, and for general corporate purposes.

In accordance with ASX Listing Rule 4.7C.3, cash paid for Directors and Non-Executive Directors in Q3 FY24 amounted to US$117k in aggregate which includes director fees and customary reimbursement of applicable costs, including costs for traveling to Opthea meetings.

Authorized for release by CEO Fred Guerard.

Enquiries

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About Opthea

Opthea (ASX:OPT; NASDAQ:OPT) is a biopharmaceutical company developing novel therapies to address the unmet need in the treatment of highly prevalent and progressive retinal diseases, including wet age-related macular degeneration (wet AMD) and diabetic macular edema (DME).

Opthea's lead product candidate, sozinibercept, is being evaluated in two pivotal Phase 3 clinical trials (COAST, NCT04757636, and ShORe, NCT04757610) for use in combination with standard-of-care anti-VEGF-A monotherapies to improve overall efficacy and deliver superior vision gains compared to the standard-of-care anti-VEGF-A agents. To learn more, visit our website and follow us on X and LinkedIn.

Risk Factors

Investing in our securities involves a high degree of risk. You should consider and read carefully all of the factors, including potential uncertainties described below, as well as the Risk Factors included in our 20-F filing for the fiscal year ending June 30, 2023 as filed with the Securities and Exchange Commission on September 29, 2023, including our condensed consolidated financial statements and related notes included elsewhere in our Half-Year Report for the fiscal period ended December 31, 2023. If any of the risks and uncertainties described under Risk Factors included in our 20-F for the fiscal year ended June 30, 2023 or the following uncertainties actually occur, it could harm our business, prospects, results of operations and financial condition. In such event, the trading price of the ordinary shares and the ADSs could decline, and you might lose all or part of your investment. You should not interpret our disclosure of any of the risks and uncertainties described under Risk Factors included in our 20-F for the fiscal year ended June 30, 2023 or the following uncertainties to imply that such risks have not already materialized.

Development funding agreement, financial resources and timing of the completion of the clinical trials

The Company had US$101.6 million of cash at March 31, 2024. Opthea believes that it will be able to fund its operating and research and development expenses through at least the third calendar quarter of 2024. As such, Opthea expects to raise additional external funding, including through equity financing, prior to its reporting of top-line data for its Phase 3 clinical trials. The amounts and timing of Opthea's expenditures will depend upon and have been impacted in the past, and may continue to be impacted by, numerous factors, including historical or future delays in completing our clinical trials, particularly as it relates to the timing of regulatory submissions, the performance and cost efficiency of contract research organizations ("CROs") and contract manufacturers, and the continuing impacts of the global supply chain and macroeconomic challenges. In particular, delays in patient enrolment have in the past resulted, and may in the future result in increased costs or delays and other impacts on the timing of our Phase 3 clinical trials. Opthea has based this estimate on assumptions that may prove to be wrong, and Opthea could exhaust its available capital resources sooner than it expects. Opthea may also experience future delays in its clinical development or commercialization of sozinibercept for wet AMD, including due to factors and conditions set forth above or other factors that Opthea cannot presently anticipate.

Opthea intends to focus its development efforts on achieving commercialization of sozinibercept for the treatment of wet AMD, and Opthea will require additional funding to reach commercialization of sozinibercept in any indication, including wet AMD. In addition, Opthea will require additional external funding to meet the minimum cash condition under the Development Funding Agreement ('DFA'), including prior to the readout of top-line results for Opthea's Phase 3 clinical trials for OPT-302 for the treatment of wet AMD. If Opthea experiences further delays in its Phase 3 clinical trials, Opthea may need to raise additional external funding, including potentially dilutive equity financing.

Opthea does not have any other committed external source of funds and expects to finance future cash needs through public or private equity or debt offerings or collaborations. However, the DFA limits the type of financing Opthea may pursue in the future and Opthea may be unable to raise additional funds or enter into such other agreements or arrangements when needed on favorable terms, or at all.

If Opthea raises additional capital, this may cause dilution to holders of the Company's ordinary shares and American Depositary Shares.

Forward-looking statements

Certain statements made during or in connection with this announcement contain or comprise certain forward-looking statements, including within the meaning of the U.S. Private Securities Litigation Reform Act of 1995. The words “expect”, “believe,” “should”, “could”, “may”, “will”, “plan” and other similar expressions are intended to identify forward-looking statements. Forward-looking statements in this quarterly report include statements regarding rapidly advancing the registrational program for sozinibercept in wet AMD, expectations regarding the pivotal growth phase of Opthea, the ability of sozinibercept to enhance vision outcomes for patients worldwide, Opthea’s expected cash runway and cash sources. Forward-looking statements, opinions and estimates provided in this ASX announcement are based on assumptions and contingencies which are subject to change without notice, as are statements about market and industry trends, which are based on interpretations of current conditions. Forward-looking statements are provided as a general guide only and should not be relied upon as an indication or guarantee of future performance. They involve known and unknown risks and uncertainties and other factors, many of which are beyond the control of Opthea and its directors and management and may involve significant elements of subjective judgment and assumptions as to future events that may or may not be correct. These statements may be affected by a range of variables which could cause actual results or trends to differ materially, including but not limited to future capital requirements, the development, testing, production, marketing and sale of drug treatments, regulatory risk and potential loss of regulatory approvals, ongoing clinical studies to demonstrate sozinibercept safety, tolerability and therapeutic efficacy, additional analysis of data from Opthea’s Phase 3 clinical trials, timing of completion of ShORe clinical trial patient enrollment and clinical research organization and labor costs, intellectual property protections, and other factors that are of a general nature which may affect the future operating and financial performance of the Company including risk factors set forth in Opthea’s Annual Report on Form 20-F filed with the U.S. Securities and Exchange Commission (the “SEC”) on September 28, 2023, Opthea’s 2024 Half Year Report included as an exhibit to the Form 6-K filed with the SEC on February 29, 2024, and other future filings with the SEC. Actual results, performance or achievement may vary materially from any projections and forward-looking statements and the assumptions on which those statements are based. Subject to any continuing obligations under applicable law or any relevant ASX listing rules, Opthea disclaims any obligation or undertaking to provide any updates or revisions to any forward-looking statements in this ASX announcement to reflect any change in expectations in relation to any forward-looking statements or any change in events, conditions or circumstances on which any such statement is based, except as otherwise required by applicable law.

Appendix 4C

Quarterly cash flow report for entities subject to Listing Rule 4.7B

Name of entity

OPTHEA LIMITED.

ABN	**Quarter ended ("current quarter")**
ARBN 672 254 027	March 31 2024

Consolidated statement of cash flows		**Current quarter $US'000**	**Year to date (9 months) $US'000**
1.	**Cash flows from operating activities**		
1.1	Receipts from customers		
1.2	Payments for		
	(a) research and development	(42,713)	(117,198)
	(b) product manufacturing and operating costs		
	(c) advertising and marketing		
	(d) leased assets		
	(e) staff costs	(3,953)	(8,415)
	(f) administration and corporate costs	(5,090)	(8,870)
1.3	Dividends received (see note 3)		
1.4	Interest received	714	2,509
1.5	Interest and other costs of finance paid	(1)	(3)
1.6	Income taxes paid	(686)	(935)
1.7	Government grants and tax incentives		5,926
1.8	Other (provide details if material)	105	247
1.9	**Net cash from / (used in) operating activities**	**(51,624)**	**(126,739)**

2.	**Cash flows from investing activities**		
2.1	Payments to acquire or for:		
	(a) entities		
	(b) businesses		
	(c) property, plant and equipment	(4)	(8)
	(d) investments		
	(e) intellectual property		
	(f) other non-current assets		

Consolidated statement of cash flows		Current quarter $US'000	Year to date (9 months) $US'000
2.2	Proceeds from disposal of:		
	(a) entities		
	(b) businesses		
	(c) property, plant and equipment		
	(d) investments		
	(e) intellectual property		
	(f) other non-current assets		
2.3	Cash flows from loans to other entities		
2.4	Dividends received (see note 3)		
2.5	Other (provide details if material)		
2.6	**Net cash from / (used in) investing activities**	**(4)**	**(8)**

3.	**Cash flows from financing activities**		
3.1	Proceeds from issues of equity securities (excluding convertible debt securities)	-	53,437
3.2	Proceeds from issue of convertible debt securities		
3.3	Proceeds from exercise of options		
3.4	Transaction costs related to issues of equity securities or convertible debt securities		
3.5	Proceeds from borrowings	-	85,000
3.6	Repayment of borrowings		
3.7	Transaction costs related to loans and borrowings		
3.8	Dividends paid		
3.9	Other (provide details if material)	(23)	(74)
3.10	**Net cash from / (used in) financing activities**	**(23)**	**138,363**

4.	**Net increase / (decrease) in cash and cash equivalents for the period**		
4.1	Cash and cash equivalents at beginning of period	157,069	89,188
4.2	Net cash from / (used in) operating activities (item 1.9 above)	(51,624)	(126,739)
4.3	Net cash from / (used in) investing activities (item 2.6 above)	(4)	(8)

Consolidated statement of cash flows		Current quarter $US'000	Year to date (9 months) $US'000
4.4	Net cash from / (used in) financing activities (item 3.10 above)	(23)	138,363
4.5	Effect of movement in exchange rates on cash held	(3,811)	803
4.6	**Cash and cash equivalents at end of period**	**101,607**	**101,607**

5.	Reconciliation of cash and cash equivalents at the end of the quarter (as shown in the consolidated statement of cash flows) to the related items in the accounts	Current quarter $US'000	Previous quarter $US'000
5.1	Bank balances	38,859	90,434
5.2	Call deposits	62,748	66,635
5.3	Bank overdrafts		
5.4	Other (provide details)		
5.5	**Cash and cash equivalents at end of quarter (should equal item 4.6 above)**	**101,607**	**157,069**

6.	Payments to related parties of the entity and their associates	Current quarter $US'000
6.1	Aggregate amount of payments to related parties and their associates included in item 1	117
6.2	Aggregate amount of payments to related parties and their associates included in item 2	-

Cash Paid for Directors and Non-Executive Directors in quarter 3 amounted to US$117k which includes salaries, travel and reimbursement of any costs.

7.	**Financing facilities** *Note: the term "facility' includes all forms of financing arrangements available to the entity.* *Add notes as necessary for an understanding of the sources of finance available to the entity.*	**Total facility amount at quarter end $US'000**	**Amount drawn at quarter end $US'000**
7.1	Loan facilities	170,000	170,000-
7.2	Credit standby arrangements	-	-
7.3	Other (please specify)	-	-
7.4	**Total financing facilities**	170,000	170,000-

7.5	**Unused financing facilities available at quarter end**	-

7.6 Include in the box below a description of each facility above, including the lender, interest rate, maturity date and whether it is secured or unsecured. If any additional financing facilities have been entered into or are proposed to be entered into after quarter end, include a note providing details of those facilities as well.

In August, 2022, Opthea entered into a Development Funding Agreement (DFA), The last tranche and option of the DFA was drawn in December 2023 for a total capital funding of US$170m. Only upon regulatory approval is the Company obligated to pay up to 4.0x the investment amount via a 7% royalty on net sales and certain milestone payments. Opthea accounts for the DFA on its balance sheet as the accreted value based on implied non-cash interest, adjusted for fair market changes if required.

8.	**Estimated cash available for future operating activities**	**$US'000**
8.1	Net cash from / (used in) operating activities (item 1.9)	(51,624)
8.2	Cash and cash equivalents at quarter end (item 4.6)	101,607
8.3	Unused finance facilities available at quarter end (item 7.5)	-
8.4	Total available funding (item 8.2 + item 8.3)	101,607
8.5	**Estimated quarters of funding available (item 8.4 divided by item 8.1)**	1.97

Note: if the entity has reported positive net operating cash flows in item 1.9, answer item 8.5 as "N/A". Otherwise, a figure for the estimated quarters of funding available must be included in item 8.5.

8.6 If item 8.5 is less than 2 quarters, please provide answers to the following questions:

8.6.1 Does the entity expect that it will continue to have the current level of net operating cash flows for the time being and, if not, why not?

Answer: The entity expects it will continue to have the current level of net operating cash flows for the time being as it continues to finalise its two pivotal Phase 3 clinical trials.

8.6.2 Has the entity taken any steps, or does it propose to take any steps, to raise further cash to fund its operations and, if so, what are those steps and how likely does it believe that they will be successful?

Answer: The entity continues to explore financing and capital structure options, as it has historically undertaken, at the appropriate time to improve its financial position. As with past practices, if its securities are still trading, it will likely be requesting a trading halt or voluntary suspension to allow it to progress any potential negotiations to a point where it can make a more detailed announcement to the market about any potential transaction. The company has a track record to securing capital at the appropriate time and funding structure.

8.6.3 Does the entity expect to be able to continue its operations and to meet its business objectives and, if so, on what basis?

Answer: The entity expects to be able to continue its operations and meet its business objectives upon the completion of any potential funding transaction along with its current cash holdings.

Note: where item 8.5 is less than 2 quarters, all of questions 8.6.1, 8.6.2 and 8.6.3 above must be answered.

Compliance statement

1 This statement has been prepared in accordance with accounting standards and policies which comply with Listing Rule 19.11A.

2 This statement gives a true and fair view of the matters disclosed.

Date: 30 April 2024

Authorised by: Frederic Guerard CEO
(Name of body or officer authorising release – see note 4)

Notes

1. This quarterly cash flow report and the accompanying activity report provide a basis for informing the market about the entity's activities for the past quarter, how they have been financed and the effect this has had on its cash position. An entity that wishes to disclose additional information over and above the minimum required under the Listing Rules is encouraged to do so.

2. If this quarterly cash flow report has been prepared in accordance with Australian Accounting Standards, the definitions in, and provisions of, *AASB 107: Statement of Cash Flows* apply to this report. If this quarterly cash flow report has been prepared in accordance with other accounting standards agreed by ASX pursuant to Listing Rule 19.11A, the corresponding equivalent standard applies to this report.

3. Dividends received may be classified either as cash flows from operating activities or cash flows from investing activities, depending on the accounting policy of the entity.

4. If this report has been authorised for release to the market by your board of directors, you can insert here: "By the board". If it has been authorised for release to the market by a committee of your board of directors, you can insert here: "By the [*name of board committee – eg Audit and Risk Committee*]". If it has been authorised for release to the market by a disclosure committee, you can insert here: "By the Disclosure Committee".

5. If this report has been authorised for release to the market by your board of directors and you wish to hold yourself out as complying with recommendation 4.2 of the ASX Corporate Governance Council's *Corporate Governance Principles and Recommendations*, the board should have received a declaration from its CEO and CFO that, in their opinion, the financial records of the entity have been properly maintained, that this report complies with the appropriate accounting standards and gives a true and fair view of the cash flows of the entity, and that their opinion has been formed on the basis of a sound system of risk management and internal control which is operating effectively.