



## Opthea Meets Primary Endpoint in Phase 2b Study of OPT-302 in Wet AMD

### CONFERENCE CALL TRANSCRIPTION

**Company:** Opthea Ltd  
**Date:** 07 August 2019  
**Time:** 9:00am AEST  
**Duration:** 1:04:49

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#### [START OF TRANSCRIPT]

**Operator:** Thank you for standing by, and welcome to the Opthea results of wet AMD clinical trial. All participants are in a listen only mode. There will be a presentation followed by a question and answer session. If you wish to ask a question, you will need to press the star key, followed by the number one on your telephone keypad. Before we get started, I would like to remark briefly on forward-looking statements. Except for historical information mentioned during the conference call, statements made by the management of Opthea are forward-looking statements. Forward-looking statements involve, and are subject to, known and unknown risks and uncertainties that are based on management's current beliefs, assumptions, expectations, and information currently available to management.

Those risks and uncertainties include, but are not limited to, risks associated with the possibility that the company's clinical trials do not meet their enrolment goals, meet their endpoints or otherwise fail such that regulatory authorities do not accept the company's application or approve the marketing of its product candidates; the possibility that the company may be unable to raise the funds necessary for the development, manufacturing and commercialization of its product candidates; that the company may not be able to develop, manufacture, and commercialise its products successfully, and other risk factors described, under the caption "risk factors", and elsewhere in our filings with ASX and US regulators.

Copies of these filings may be obtained from the company. Forward-looking statements are not guarantees of future performance and no assurance is given that the results, performance or achievements expressed or implied by forward-looking statements will actually occur. Accordingly, undue reliance should not be placed on forward-looking statements. I would now like to hand the conference over to Dr Megan Baldwin. Please, go ahead.



**Megan Baldwin:** Thank you, Jennifer. It's Megan Baldwin, CEO and Managing Director of Opthea, Limited, and I will be responsible for the first part of this call. So thank you very much, everyone. Good morning, and thank you for joining today's teleconference. Before we begin I would like to confirm that a transcript of today's call will be made available on Opthea's website at [www.opthea.com](http://www.opthea.com) within the next 24 to 48 hours.

Also, it is my pleasure to introduce both Professor Tim Jackson and Dr. Pravin Dugel, who will participate in today's call from their respective locations in London and Phoenix.

Professor Jackson is a consultant ophthalmic surgeon at King's College, London, and chief investigator on the Opthea phase 2B clinical trial. In his role, Professor Jackson was involved with the study design and the assessment of the current top line results announced today. He will be available during the Q & A session later in the call.

Dr. Dugel is a Clinical Professor at the University of Southern California Roski Eye Institute, Keck School of Medicine; and Managing Partner of Retinal Consultants of Arizona. Dr. Dugel is a principal investigator on the Opthea Phase 2B wet AMD study and ongoing Phase 2A study in diabetic macular edema. He also participated in Opthea's previously completed first in human wet AMD trial. In a few minutes, I will hand over to Dr. Dugel, who will provide his clinical perspective of the therapeutic potential and commercial opportunity for OPT-302 in retinal disease indications based on the exciting efficacy results from the Phase 2B trial.

Today's announcement of positive efficacy data for OPT-302 combination treatment in achieving superior gains in vision, over the anti-VEGF standard of care monotherapy, is a tremendous outcome for Opthea and provides a hope of a new therapeutic approach for patients suffering with wet AMD, a leading cause of blindness. We sincerely thank all of the patients, investigators, and the site staff, for their participation and helping to make the trial a success.

For those of you who are new to Opthea, I just want to provide a brief background on the opportunity of our treatment approach.

Standard of care therapies for wet AMD and other retinal vascular diseases, including diabetic macular edema, share a common mechanism of action, by inhibiting vascular endothelial growth factor A, or VEGF-A, a key mediator of vascular development and permeability, which can lead to vessel leakage and edema formation.

In the last decade VEGF-A inhibitors including Lucentis, Eylea and Avastin, have transformed the treatment paradigm for wet AMD patients. Yet while these anti-VEGF-A monotherapies have been shown to stabilise disease and improve vision, there are many patients in whom anti-VEGF injections are not sufficient to achieve or maintain significant improvement in visual acuity over time. Hence, there is a need for new treatments, to improve the clinical management of wet AMD over and above what can be achieved by targeting VEGF-A alone.



Opthea's lead drug candidate, OPT-302, is a soluble fusion protein that is formulated as a solution for intravitreal injection. It blocks the activity of two alternate members of the VEGF family that are distinct and different to VEGF-A- namely, VEGF-C and VEGF-D. These factors have also been shown to be important mediators of angiogenesis and vascular permeability, and have been implicated in contributing to the suboptimal clinical responses in many patients who receive selective VEGF-A inhibitors. OPT-302 is the first trap inhibitor of vascular endothelial growth factors C and D, specifically designed for the eye.

The Phase 2B trial, which was initiated in December of 2017, is one of the largest randomised, controlled, Phase 2B studies ever conducted in wet AMD. The study enrolled 366 patients who had not received prior therapy and were therefore treatment naïve. Patients were recruited across 113 clinical sites in ten countries in the United States, Israel and Europe.

The prospective, controlled, double-masked trial was designed to demonstrate the safety and superior efficacy of adding OPT-302 to Lucentis standard of care therapy over a 6 month dosing period. Patients were randomised in a 1:1:1 ratio to receive one of the following treatment regimens, administered by sequential intravitreal injections, administered every four weeks for 24 weeks:

- OPT-302 at a dose of 0.5 milligrams in combination with Lucentis at 0.5 milligrams
- OPT-302 at a dose of 2 milligrams in combination with Lucentis at 0.5 milligrams,
- Or a sham control in which a sham injection in combination with Lucentis at 0.5 milligrams was administered.

The entire team at Opthea is delighted to report today that the Phase 2B clinical trial met the pre-specified primary endpoint of demonstrating statistically significant superior gains in mean visual acuity at 24 weeks in patients treated with 2 milligrams OPT-302 combination therapy compared to Lucentis monotherapy.

These results truly position Opthea well-ahead in the competitive landscape of other companies developing new therapies with novel mechanisms of action for the treatment of wet AMD.

Secondary endpoint results were also supportive of the primary outcome. These included an increased proportion of patients gaining ten or more letters and fifteen or more letters from baseline, and a higher number of patients with stable vision at week 24 compared to baseline, in the 2 milligram OPT-302 combination treatment, compared to Lucentis monotherapy.

Our results today bode well for the commercial potential of OPT-302 and we are truly excited about the potential of OPT-302 to change the treatment paradigm for wet AMD patients.



Patient demographics and lesion characteristics were well-balanced between the treatment groups. 95% of patients enrolled into the trial completed the study, and study compliance overall was high.

And now to the specifics of the data:

Patients receiving the combination of 2 milligrams OPT-302 and Lucentis had a mean gain in visual acuity from baseline to week 24 of 14.2 letters, compared to a gain of 10.8 letters for patients receiving Lucentis monotherapy, resulting in a statistically significant benefit of 3.4 letters for at a p value of 0.0107.

Low dose OPT-302, at 0.5 milligrams combination therapy, showed a similar response to the Lucentis control group with a mean gain in visual acuity of 9.4 letters at 24 weeks.

Looking further at the 2 milligrams OPT-302 combination group more closely, 45% of patients gained 15 or more letters from baseline to week 24, compared to 40.5% of those in the Lucentis control group. The proportion of patients gaining ten or more letters was also greater, at 70% versus 57.8% respectively.

Stable vision, defined as a loss of fewer than 15 letters from baseline, was maintained in 99.2% of patients receiving 2 milligrams OPT-302 combination therapy, compared to 96.7% in the Lucentis control group.

Intravitreal OPT-302 combination therapy was also well-tolerated, with a similar safety profile with that of Lucentis. The independent Data Safety Monitoring Board, or DSMB, confirmed that no new safety risks were identified in patients administered OPT-302 combination with Lucentis, compared to those patients administered Lucentis alone.

We now have extensive global clinical dosing experience with repeated intravitreal administration of OPT-302 in well over 400 patients across three international clinical studies in two disease indications, demonstrating a favourable safety profile.

Taken together, these compelling results clearly support advancing OPT-302 into pivotal registrational Phase 3 development. We firmly believe that OPT-302, which was designed specifically for the eye as the first 'trap' inhibitor of VEGF-C and VEGF-D, which are part of the most validated target pathway in back of the eye diseases has considerable potential to improve outcomes in wet AMD and other retinal vascular diseases.

We will provide an update on future development plans in due course, once we've completed further data analysis in the Phase 2B trial, which we are fully committed to presenting at upcoming major ophthalmology conferences.

In addition, we are also excited with the progress of the clinical development of OPT-302 in the second disease indication, diabetic macular edema or DME. Patient recruitment is nearing completion for our ongoing Phase 2A clinical trial of OPT-302 in combination with



Eylea for the treatment of persistent central-involving DME. The clinical benefit observed in the Phase 2B wet AMD trial support our strategy for also targeting diabetic retinopathies and bode well for similar outcomes in the Phase 2A DME trial.

I'd also like to quickly comment on the company's financial profile. Opthea is in a strong cash position with approximately 20 million Australian dollars cash in bank, and an additional approximately 14 million dollars from an anticipated R&D tax rebate later this year. We are also in the fortunate position of having the Phase 2B top line results available six months ahead of schedule, and this has led to substantial cost savings for the company. We are fully funded through remaining Phase 2B trial close-out activities and the completion of the ongoing Phase 2A study in DME. In addition, the company has sufficient capital to prepare for registrational Phase 3 trial activities and to evaluate all strategic and corporate options.

Before turning the call over to the moderator to commence the Q&A portion of today's call, we have Dr. Dugel on the line, who will now provide some comments on today's results and his perspective on how OPT-302 fits in the wet AMD treatment landscape.

Dr. Dugel, over to you please.

**Pravin Dugel:**

Megan, thank you, for including me in this wonderful meeting. I'm just absolutely delighted to be here and having worked with this company from the very beginning. What I'd like to do is to provide you a perspective as a clinician first, and then as a clinician investigator. As a clinician, I'd like to provide you with a perspective of how this may affect my patients. I'm old enough to have seen the entire anti-VEGF-A renaissance and revolution. I know the impact that that's had on my patients, but I'm also objective enough to know what the unmet needs are, and if anybody were to say, "What is the largest unmet need," it would be efficacy. There's no doubt about that whatsoever. Durability is important, sustainability is important but there's nothing that's more important, or more challenging, or higher bar, than efficacy.

It matters to my patients whether they can drive. It matters to my patients whether they can read their chequebooks. It matters to my patients whether they can live independently and cook and walk, et cetera. That's extraordinarily important. And if there's a drug that I can give my patients to improve efficacy and allow them those privileges that they're used to, of living independently, of driving, of being able to write a letter, of being able to email, of being able to walk and look at the computer; that's a huge, huge improvement in their quality of life. So, this medication potentially would be able to improve the quality of life in all of my patients and fit an unmet need that is the largest unmet need that we have. So, that is how I look at all this from a clinician perspective.

From a clinician investigator, or from a clinician scientist perspective, a lot of the companies that I know of have looked at efficacy as a bar that's simply too high. Everybody realises the unmet need, but anti-VEGF-A monotherapy is so effective that in order to improve efficacy beyond anti-VEGF-A monotherapy is a daunting task. And they have failed. And I'm really



happy that we have a drug here that has the potential to allow us to go beyond that bar that's been set. This is really the first trial that I know of in a very, very long time or historically that has actually improved the efficacy of anti-VEGF-A monotherapy. And that is a much, much more difficult task, a much higher bar than improving durability.

And note that there's still a potential, certainly, of improving durability because if you improve efficacy it would make sense that you'd have to treat less. But that wasn't the point of this study. The point of this study was to see if this will actually improve efficacy, and that endpoint was met. Intuitively angiogenesis is a complicated process. Just intuitively, you know there can't possibly be simply the one ligand that's responsible for that. So, it makes sense that there are other mechanisms of action, and this is the first time that a different mechanism of action that is complimentary has been shown to be effective and actually better-combined than anti-VEGF-A therapy alone.

That's something that, in my mind, is almost the Holy Grail that we've been thinking of for a very, very long time. And finally, the part that really appeals to me also is that there are many new drugs, as you know, that are the next generation of anti-VEGF-A drugs, that are better than the ones that we have today. This drug is agnostic of these anti-VEGF-A drugs. It works independently, it provides an entirely different mechanism of action and it's absolutely complimentary to the anti-VEGF-A's that are being developed. So for all those reasons, as a clinician and as a clinician scientist, I'm delighted to be here and very, very excited in this historic day. Thank you. Back to you

**Megan Baldwin:** Thank you, Dr. Dugel. At this time we'll turn the call over to the moderator to enable the Q&A portion of today's event to begin.

**Operator:** Thank you. If you wish to ask a question, please press \*1 on your telephone and wait for your name to be announced. If you wish to cancel your request, please press \*2. If you are on a speaker phone, please pick up the handset to ask your question. Your first question comes from Shane Story from Wilsons. Please go ahead.

**Shane Story:** Thanks for taking my question. First is obviously, we're seeing a really strong signal on the 2 milligrams dose but how should we think about having not seen one at the lower 0.5 mg dose? I understand there's some statistical implications of that, but are there any other ways that that might influence Phase 3 and the regulatory outlook from here?

**Megan Baldwin:** Thanks, Shane. Thanks for that question. It's a good question. We anticipate that we'll be moving forward with the 2 milligrams dose in future clinical studies. Certainly the safety profile that we've observed across over 400 patients now would support us moving forward with that 2 milligrams dose, given that the safety has been so very clean and well-tolerated. In terms of the dose response, it's something that we're going to dive into in much more detail. As you can appreciate, this is topline data that we have available now. We don't currently have our pharmacokinetic analysis data available at this point in time. That's data that will come through over the coming weeks and months and we fully intend to dive into

that data and more completely understand the pharmacokinetic profile at that dose. And also, to dive into the full data analysis.

Certainly, we didn't see a difference with the 0.5 milligrams in the mean change in BCVA or visual acuity, but there's a number of other secondary outcomes and exploratory endpoints that we can dive into to fully explore any activity with the 0.5 milligrams dose as well.

**Shane Story:**

Thanks. Look, second question I had was the responses in the trial were probably the highest I've seen for Lucentis and I was just wondering if you could comment more a bit about the patient phenotypes, particularly the spread of lesion types that you recruited across the occult, the classic and the minimally classic, just to try to understand how high those responses were?

**Megan Baldwin:**

Yeah. Absolutely. You're correct. I'm going to hand over to both Tim and Pravin to comment on this but I'll just say a couple of comments. So, this is historically I believe the highest Lucentis control over a 24 week dosing period where Lucentis is administered on an every four week dosing cycle. 10.8 letters is an exceptional response for Lucentis, and so the bar was set high for statistical significance compared to that.

In terms of the lesions and the patient demographics, firstly I'll say that they were very well-balanced across the treatment groups. The spread between predominantly classic, minimally classic and occult lesions were also well balanced between all three treatment groups, and the profile of the percentage of predominantly classic, minimally classic and occult patients was what we would expect from a real world population, if you will. Approximately in the range of 10-15% for predominantly classics and around about 42-44% for each of the minimally classic and occult lesions.

That kind of demographic data and a further understanding of all that demographic data, will be presented in an upcoming ophthalmology meeting. Perhaps I'll ask you, Tim, to also comment a little bit about the control here just to answer Shane's question in a little bit more detail. And then, Pravin, perhaps you can also comment.

**Tim Jackson:**

I think you've made the key points. The patients look like patients that we see every day, in terms of age and sex and ethnicity. And also, the lesion types. Interestingly, there's always a lot of discussion about whether it's classic or minimally classic and occult, and in a way that's becoming slightly less important nowadays because they're all treated with anti-VEGF-A. But having said that, there were no surprises in terms of the case mix between those. So I think it worked across the board. It wasn't as if we had to go for subgroup analysis to find it working. It worked at all times. As Megan said, there was a good balancing between the arms. The control group is very interesting, and it's one of the things that really strikes me, when you look at the data is that the control group did extremely well. And we all know that the trial patients in the control arms tend to do better than they do in the real world. So, we do expect to see good divisions, but even so that was really very, very high. And I think that, if anything, speaks to the efficacy of OPT-302 because to get a positive result against that

kind of a Lucentis arm is not easy at all. And I know when we were designing this study that the treatment with monthly Lucentis, it's pretty hard to beat that. And harder still, if you end up with plus 10 letters or so. So I think if anything, if we had a more typical control arm of visual acuity, you may see the margin difference would probably increase. Pravin, any thoughts?

**Pravin Dugel:**

Yeah, I completely agree with what has been said. And, as you may know, I do due diligence for a lot of companies all the time. And, when we do due diligence for a drug, we usually look at the delta. And sometimes what we forget is to say, well what is the lower part of that delta and how does the control arm perform? And as you all know, there are lots of drugs that we can think of that have gone to a larger trial where that delta hasn't been borne out because the control arm may have underperformed. Well, that's something you never have to worry about here, because this is the best performing control arm that I've seen. And for whatever reason, that's what happened. And at the end of the day, if there's a delta with the best performing control arm and the bar is as high as can be, you can be darn sure that that delta is real, and that delta probably will be much greater if the control arm behaves as it should have, or as expected.

So, I go back to this Phase 2 trial and say, what is the Phase 2 trial supposed to show? It really is supposed to show only two things, the first thing that it's supposed to show is safety. And the second thing is that it is supposed to show is a biological signal. And I think that there can be absolutely no doubt whatsoever that those have been shown. And again, the second part about the safety, given the control arm performing as well as it has, that you're able to show a delta should give a great deal of comfort that if the control arm had performed as would be expected, that delta would be even greater. So again, that that gives me a great deal of confidence in the results.

**Shane Story:**

Hey, thanks. The last question then I've got, the press release just implied also that less patients sort of lost vision. I was just wondering if you could share any specific stats on that observation.

**Megan Baldwin:**

Oh yeah. We didn't include a lot of the quantitative detail included in there, but it was quite profound. Obviously the rate of stable vision itself was very high in the trial. However, it was very encouraging to see that in those patients that don't do well, there was a marked improvement in those patients that ... In the proportion of patients that didn't lose vision, if you'd like, that actually had stable vision. The exact numbers, Shane, we'll put out in a subsequent presentation at a medical conference, but it looks like we're gaining vision in gainers but also improving outcomes for patients that would otherwise lose vision. Is there any further comments perhaps from you, Tim being so close to the data in terms of your observations around that point as well?

**Tim Jackson:**

Yeah, what you said is very true. Well, again, when we were thinking about the design of the study, there was really sort of, we had a debate as to whether or not this drug is going to work by reducing the loss of vision. And that might be how you might imagine it working if



we're trying to target poor responders or non-responders, of which there is a huge number of patients who don't do well. Or is it going to work by enhancing vision gain? And of course there's overlap, but there are slightly different potential sort of approaches. And the data we saw was driven by increased visual gain. Hence, if you come back to the absolute number, this is a patient population gaining 14 letters, which is huge.

They were a very small proportion of patients who lost significant amounts of vision. So actually, it's harder to pick up on a signal like that. But interestingly, even though those small numbers of patients weren't driving the overall result, but the trend was definitely there, that there was not only improved vision gain but there was reduced vision loss. And I think that will be what plays out if this does get to market, that's what you're looking for. You're looking for a drug that can offer better vision, and that is making the earlier point in terms of what that means day to day for patients, but also looking to talk to those patients who otherwise are not doing well. And as time goes by we are increasingly aware of the fact that there are a significant proportion of patients who could lose vision despite good compliance and, and regular dosing.

**Shane Story:**

Thanks. That's all the questions I had.

**Pravin Dugel:**

This is Pravin. I would completely agree with Tim. And essentially, the way I would look at this is that these things are interdependent. The gain in vision and the lack of loss of vision aren't two different silos, but they are absolutely related. So, if you have more patients that gain more vision, certainly we'll have less patients that are losing more vision. What this drug does is it allows the needle to move very much to the right. And what does that mean? And again, I just want to go back to telling you what that would mean to the day to day physician like me who's a clinician that sees patients during the week. When a patient comes to see me, that patient may be driving, may be living independently, may have been writing their own chequebooks, may have been emailing their granddaughters and grandsons, and then they come to see me with a catastrophic loss of vision.

So let's say they were 20/40 and they come to see me with a visual acuity of 20/400. So, when I see those patients, they're 20/400 and then I look at that patient and say, Mrs. Smith, I'm very happy to tell you that we actually have something that we can give you to help you. This wasn't the case just a few decades ago, but now I can give you something. You have to come every four weeks, but I can help you. And when I started giving her the injections, I see her at 20/40 and I have a great success. If I can improve that patient from 20/400 to 20/100 or even 20/80. And from my perspective, that's a fantastic success. From her perspective, she still can't drive. She still can't do her chequebooks. She still can't write an email to her granddaughter and grandson, and she's still can't live independently. So to be able to have this drug that will actually improve efficacy and possibly for 15 letters, which is three lines, which we really have dreamt about, but have never really come close to achieving, is a monumental achievement and a monumental delta for my patients. If my patients can now live independently, drive, do their chequebooks and so on and so forth, and this drug will

push them to be able to do that. It certainly will be used. And it certainly will be very impactful in my clinical practise.

**Megan Baldwin:** Alright, thanks.

**Tim Jackson:** One point I would add to that as well, I mean, the question that patients want to know when you ... they'll say to you, we'll talk through the different drug options that are available at the moment, which is Avastin, Eylea and Lucentis, and the question most patients will ask is well, which is the best? And visual acuity is how we measure efficacy. So if we've got anything that improves the vision and becomes the best treatment, then it will find a market.

**Megan Baldwin:** Absolutely. All right. Thanks Shane for those questions and thanks Professor Jackson and Dr Dugel.

**Shane Story:** Thanks everyone for your answers. That's very helpful. Cheers.

**Megan Baldwin:** Thank you.

**Operator:** Thank you. Your next question comes from Craig Colley from Regal funds. Please, go ahead.

**Craig Colley:** Thank you very much and congratulations Megan. A fantastic result, very excited for the company and also exciting day for sufferers of this very common disease. I've got three questions. One for you, Megan, if that's all right, and three for the experts. Yeah, I guess first for the experts, and you just touched on this in your previous answer, but I believe the ... on the primary end point, there were 3.4 letters of improvements between the treatment and control groups. Can you guys just comment on the clinical significance of that? Is that a meaningful improvement for your patients or, yeah, some colour on that would be fantastic. Thank you.

**Megan Baldwin:** Thanks ...

**Pravin Dugel:** So this is Pravin ... I'm sorry Megan, go ahead.

**Megan Baldwin:** Oh, go ahead, sorry.

**Pravin Dugel:** Oh, I'm delighted to comment on that and you know, look at how comments on it from the clinical trial's perspective and a drug development perspective and then I'll comment on it from the clinician's perspective. From a clinical trial and development perspective, there are many drugs that have got ... that have been developed with far less delta than that. And the fact of it is that amount of a delta, can be very clinically meaningful. Remember, that what you really have is a bell curve and you're looking at the median at the bell curve. There are a lot of people that are right at that bell curve and what you'll see here is a top line data analysis that ended up significant. We still have to dive deep into the data and look at the

variability of this outcome. Look at the entire data set, and look at those patients that responded really well.

And those patients that may not have responded well, may have is my feeling, may have been patients that have already been recruited with really very good vision and they have a had a ceiling effect. But, you get meaningful, absolutely meaningful ... from a clinical trials perspective, again, when you think about that bell curve, and when you think about the people on the right of that bell curve, it is absolutely meaningful. And that's my clinical trials perspective. From a clinician's perspective, the difference, if you can get three letters, or even if you can get five letters. If you get six letters, or even if you get two letters, may be the difference between driving and not driving. May be the difference between seeing the chequebook, and not seeing a chequebook. Is that meaningful? Absolutely. And would I use that? Certainly, I would, because I know that what I want to do to give my patients the very best vision that I possibly can from the very beginning.

And personally, I'll tell you that my father is 89 years old. He's got macular degeneration. He's got a disciform scar in one eye. He's been treated for the last 15 years, to the extent of every four weeks in the other eye. And thank goodness he maintains a vision of 20/25. Would it be helpful for him to have a little bit better vision? Absolutely. Well, it would mean that he can see the TV better, it would mean that he can write his checks better. It would mean that he can, you know, look at his TV better. So it is very meaningful. At the end of the day we'll analyse those patients that did the best, but remember, it's a bell curve and it's very meaningful for clinicians, and this is certainly a delta that one looks at and says this will impact my patients.

**Megan Baldwin:** Tim?

**Tim Jackson:** Yeah I would echo those comments. I think the interesting point is that people do want the best treatment. And if it allows them to give a bit better treatment then that is what they will want. If you're being terribly cynical, then another key issue is that the sustained release drugs, as they emerge, and that's in many ways, much of the discussion is about having a drug that lasts longer. But you know, in not so much the UK but in countries where people are paid to inject, there's an obvious paradox there in a sense. They want to give the patient the most convenient treatment, but of course they lose money if they're not injecting regularly. And the clear message to the patient is that, we might have to inject you a little bit more often, but we can offer you a better vision. And I believe it is a meaningful core difference.

The clinicians may well be driven to say, well look, they are going to get a personal benefit by injecting more often. I know that is a horrible thing to say, but those things do influence the market. So, I think if the clinician is able to say this is a better drug or it's a better combination treatment, then I think they'll be inclined to promote it. I think ... proving the point that small differences in terms of measured acuity can make a big difference, but these are group means, these are not individual means.

And if you look at the median, which in some ways is more telling, that's happening to your average patient rather than a few outliers that's being driven by the group as a whole. And those are the ones that represent the bulk of the patients. And actually when we get to release those, I think we'll see ... we'll have more insight into what that delta is.

I think we have got the option as Pravin says, refining our case selection. But actually ... most trials as you move forward, you learn better the patients to target. And I would predict, this is a big enough study to learn a lot about which are the right patients to target. So, I think going forward, with the knowledge that we've gained from the study, from a fairly in depth analysis, if you had to make a prediction my expectation would be as a larger study would get a bit better vision knowing what we do now.

**Megan Baldwin:** Craig, did you have another question?

**Craig Colley:** Yes. Thanks guys, that was fantastic. Second clinical question please is I mean, no one's got a crystal ball obviously, but, I'd love to hear your comments, guys about the potential read through for this drug in the diabetic macular edema setting?

**Pravin Dugel:** So, what I would say is that if you look back and see the physiology of wet AMD and diabetes and retinal vein occlusion, those drugs that have worked in one have worked in the others. And I'm very, very hopeful that this will work, not only diabetic macular edema, but diabetic retinopathy and later on retinal vein occlusion and other things as well. I see no reason why it should not, because the physiology is really the same in terms of stabilising the vessels in terms of preventing leakage, in terms of shutting down the redundant pathways. And the thing that I really like about this, is that there is a mechanism of action that has a great deal of preclinical studies that have been done in oncology and in other fields, regarding redundant pathways and what we're seeing now is the clinical results that we expect to see, given the preclinical studies that have been done. And it's always very nice when everything is sort of pointing in the same direction. And at this point, we've gotten great results in wet macular degeneration and history would suggest that given the mechanism of action, there's no reason we shouldn't get equally good results in DME, DR, retinal vein occlusion, myopic choroidal neovascularisation and other things that have been used.

**Craig Colley:** Great. Thank you very much. And then switching to you, Megan. Yeah. I guess the question is, maybe it's too early to ask this, but you know where to from here? You mentioned that you're likely to push forward with the two milligrams dose, but any thoughts on what the phase three might look like? Thank you.

**Megan Baldwin:** Yes. In terms of the phase three, I mean we have a good understanding what our registrational programme would look like in that, but what I will say is that on the back of these results, obviously we'll move forward with looking at that programme and designing that with the input of the US and the European regulators. And we can move forward with that now, knowing that we've got good solid proof of concept data from a phase 2B setting. And obviously as we remarked in the announcement, we have sufficient capital in order to



be undertaking those preparatory activities for the phase three programme as well over the coming months. So we're really well positioned to be able to now design the phase three programme and look at all of the strategic options for the company.

**Craig Colley:** Okay. That's great. Thanks for all your answers and congratulations again.

**Megan Baldwin:** Thanks, Craig.

**Operator:** Thank you. Your next question comes from Tanushree Jane from Bell Potter Securities. Please go ahead.

**Tanushree Jane:** Hi Megan. Congratulations. I think this is a really, truly remarkable day for a lot of people suffering from these debilitating diseases. So, congrats. Just a few from me. Just in terms of the proportion of patients who gained more than 15 letters, you've mentioned you've seen a reasonable proportion of patients who performed better with the combination treatment with OPT-302, did you do an exercise to see people who would have perhaps gained more than four lines or five lines? What kind of differences were at that level?

**Megan Baldwin:** Obviously yes, we can go through the full data analysis when it becomes available. We don't have any of that data right now, because we have to be quite selective in what was reported out in our top line. But certainly, we can get information on any sort of quartiles or threshold levels that we wish to analyse the data at any level.

**Tanushree Jane:** Okay, cool. But I'm assuming you would've seen some trends, you would have some idea as to how that went?

**Megan Baldwin:** No, because it's not in the top line data. The top line data readouts did not include the 20 or 25 letter data.

**Tanushree Jane:** Okay. The 20 and 25 okay. And did you do a mean change at week 12 as well?

**Megan Baldwin:** We have a lot of information across all different time points for the data outputs that were included in the top line data. As I said, we saw a separation of the curves as early as eight weeks as you can see on the graph that was included in the ASX announcement. So it, ... the separation occurs very, very early in this dosing regimen. So yeah, we've got a lot of information across different time points, and that'll all bear out in further detailed presentations at conferences coming up.

**Tanushree Jane:** Right, and ...

**Pravin Dugel:** This is Pravin, and I think your question is a really important one, and I just wanted to interject in terms of planning for the phase three. There are several things here that should give us a great deal of confidence in terms of us planning for the phase three. One that we've already discussed, which is how the control arm performed, which I think is an anomaly in terms of performing as well as it did. So, if it performed as one would expect,

again that delta would be greater, and one would expect that in phase three, I guess because of regression to the mean, and because of the numbers the control arm wouldn't probably perform as we expected. But in of itself, that's should give us a great deal of confidence that in a larger study, in a phase three study that that delta maybe even greater.

But to your question, which is are there patients that gain maybe four, five, six lines of vision, they probably are. And I'm sure there are, because it's a bell shaped curve. And the other part that one should look at in terms of the phase three confidence is that with this large phase two study, we can analyse it in a post hoc manner, and then go ahead and study those patients in phase three that may have done particularly well. For instance, there may be patients in phase two that simply were recruited with vision that was very good that hit the ceiling, and simply couldn't improve any further. So learning those things from phase two, we can translate that into phase three, and then have an enhanced patient population. And I think that's what you're referring to, which actually would give us even better results. So, if you think about one is that the regression to the mean of the control arm, given the larger phase three study and the other, is a better understanding what the patient population that performed very well, you can look at that and say, if we design the phase three properly and get the advantage of the knowledge that we have from phase two. You can really expect that Delta could be even greater and that should give us a great deal of confidence.

**Tanushree Jane:** Great, thank you. And just another question on the OCT imaging on the retinal thickness. Would you comment on how was that for the Lucentis alone or was that in line with what you've historically seen or did we see that being better in this trial as well?

**Megan Baldwin:** Tim, do you want to take that one or I can.

**Tim Jackson:** Yeah, sure. Well, the press release has a lot of that information in it. If you look at it in terms of the numbers that they given there. So a 134 micron reduction. The OCT is a pretty good response in that fits with a very good visual acuity response. I don't think there were any surprises in that. I mean the OCT is actually very interesting because although there was a greater reduction in the fluid in the OPT-302 dosing, two milligrams dosing group. So there was a structural benefit. The OCTs were, I think effectively really quite dry. So it's hard to show much of a difference between the two. And my hunch is, from looking at the fact that the vision was so good and yet the OCTs were relatively typical in that sense, I think that the drug is working in a different way.

And we always sort of assume that the OCT and the visual acuity will be roughly in sync. I mean, we know they're not always, there can be a lag, there can be discrepancies. But there does seem to be interestingly a bit of a disconnect between the two. So I think we're learning more about the way they just see and how does suppression work. And I think we're going to find out that maybe working, not just through drying out the fluid, but maybe anti inflammatory, maybe something else. So I think that speaks to the novelty of the drug. That it's not just about drying up the OCT even though it does seem to do that.



**Megan Baldwin:** Yeah, and I'll just add on that point also, there's a number of different anatomical outcomes that we don't have in our top line data. We have, for example, central retinal thickness and further data around subretinal fluid and obviously we'll dive into that when that data is available, as well.

**Tanushree Jane:** Right. And just on this result, is there any readthrough for perhaps the prior treated but not responsive patients on anti-VEGF-A?

**Tim Jackson:** Megan, do you want me to comment?

**Megan Baldwin:** Go ahead. Yes, please.

**Tim Jackson:** So I think that the trials tend to focus on treatment naive patients. That gives you, if you like, the purest data. So I think it's the right thing to do methodologically. But as we know from all the previous trials that the patients are tested on, the drugs are tested on treatment naive patients. But then they're often rolled out in the real world to previously treated patients. So I think, you know, almost certainly if this drug went to market, it wouldn't be reserved just for treatment naive patients. Like, you know, with certainty it would be used in the pool of patients who are already in the clinics. In terms of it being a particular useful drug for those who are not responding. That comes back to the comments I made earlier on. I think it very much will be.

And we did have a hint of that in terms of the loss of vision. Even though there were small numbers of patients losing vision, there was a difference and actually a very large difference in terms of proportions. Even if not in absolute numbers, a greater proportion of patients didn't lose vision in those treated with OPT-302. So I think almost certainly it would be used in previously treated patients and I suspect it may be particularly good. But we'll need more data to confirm that. But I suspect that we'll find a wide market.

**Tanushree Jane:** Great. Thank you.

**Pravin Dugel:** Thanks for doing that. And I agree with you, Tim. You know, I look at this and regarding the question that was asked earlier on about the OCT, we know that OPT-302 does have an anti-permeability effect and when I look at it with the OCT results is that the OCT results are good as they can be. And in order to go ahead and improve the vision consistently, statistically significantly as this drug has done, there's got to be other mechanisms of actions as well in addition to the anti-permeability effect. Clearly there is.

Unfortunately, we just don't have a biomarker to measure those. But given those things, and if the question is how would you use this drug? If I had it in my hands, and I certainly would use it on patients that were treatment resistant and we have lots and lots of those patients because I would look there and say, well, the anti-VEGF-A has done all it can and there's an added benefit here that's agnostic of the anti-VEGF-A that I'm using, whether I'm using Eylea or Lucentis or Avastin, so even on those patients. But also I wouldn't limit myself just to those patients.

I certainly would use it, absolutely on patients that were treatment naive. And I look at this and I say, why would I deny my patients extra improvement in visual acuity from the get go, from the onset. There's also some evidence that if you have fluid there for a longer period of time in a lot of these chronic diseases, including wet macular degeneration, but certainly DME and RVO and so on and so forth, that you may not have, the patient may not recover to their best potential if they're switched later to the most appropriate treatment that gets rid of the fluid and gets the improved vision.

So in other words, if the treatment, if it is switched, the most appropriate treatment is then delayed, that patient may or may not get to the potential visual acuity improvement the patient can get to. So with that in mind, I certainly would start treatment naive patients on the very best regimen that I could possibly find. So I think what you would see is that this drug would be added on patients that were treatment resistant and we have lots of those patients, but certainly wouldn't be just confined to that. I think I would also look at patients that were treatment naive and say from the get go, "I'm going to go ahead and give you the very best combination I can in order to optimise your visual potential."

**Tim Jackson:**

I was just going to add one thing. I mean one of the interesting points is that we've tested this drug with Lucentis, which is a natural partner and methodologically, I think it's the right one to use, but of course there's no reason why it can't be used with other anti-VEGF-A drugs. And of course if you, if you might test it with Lucentis, but almost certainly it would end up being used with other anti-VEGF-A drugs with or without a different trial with different anti-VEGF-A agents. That's just the way it will be used clinically. But one of the interesting things is if you suppress VEGF-A, you possibly probably push up VEGF-C and VEGF-D. You know, we know that from some of the early studies and it seems like that's what's happening clinically.

And interestingly, if you look at the visual acuity graph, there is a bit of a lag as if the first study point at four weeks, there's not much of a difference between them. And then all of a sudden there's this big difference opens out. And one hypothesis is that basically, you know, the VEGF-A kicks in. It works, and then VEGF-C and D pop up. There's a response that works against the effects of VEGF-A. And that's when you start to see the benefits of OPT-302. Now of course if we bring in better anti-VEGF-A agents and there's lots of anti-VEGF-A agents making their way through, the more you suppress VEGF-A, the more you may push up VEGF-C and VEGF-D and the more you may need a second drug to counteract that effect.

So I think it will work in treatment naive and in previously treated patients, but I also think it will work across a range of anti-VEGF-A drugs.. Whereas this is a totally new approach to treatment.

**Speaker :**

We need to go to the next question if that's okay.

**Megan Baldwin:**

That's fine. Thank you.



- Operator:** Thank you. Your next question comes from Dennis Hulme from Taylor Collison. Please go ahead.
- Dennis Hulme:** Oh, hello. And congratulations very much on the results. Dr. Dugal has answered most of my questions. But I guess about the registration programme. Looking forward, do you anticipate that there'll be just a single phase three study required for registration or might you need to do two phase three studies? Have you had any feedback from the regulators about that?
- Megan Baldwin:** We haven't specifically gone to the regulators at this point in time. We would go there with the phase 2B data in hand as you can appreciate Dennis, but we would anticipate two phase three registrational studies that will be run concurrently.
- Dennis Hulme:** Okay. Thank you very much. That's all from me.
- Operator:** Thank you. Your next question comes from Carlos Montagna. Please go ahead.
- Carlo Montagna:** My questions have been answered already thank you. Congratulations Megan, by the way, and the Opthea team.
- Megan Baldwin:** Thanks Carlo.
- Operator:** Thank you. Your next question comes from Nicholas Sandridge. Please go ahead.
- Nicholas Sandridge:** Yes, again you answered quite a lot of my questions and once again, congratulations on your results. I've just got one question. Does this change anything in regard to your plans for commercialization? It certainly gives you proof that this thing works, but will it make a difference to your plans in terms to bring commercialization forward sooner than what you might have previously anticipated.
- Megan Baldwin:** Oh look, I think we are highly encouraged by the data that we've read out today, and I think we're very much encouraged to move it forward for the benefit of patients as expeditiously as possible. So, the programme as we've always undertaken, is to move things forward as efficiently and as effectively as we can. And certainly we're really excited about it. And we're going to move forward with all of the planning that we would need to undertake for the registrational programme as well. And also we're eagerly awaiting the data from the DME trial, so we're actively progressing with that one as well.
- Nicholas Sandridge:** All right, thank you.
- Operator:** Thank you. Your next question comes from Chris Keller from MST. Please go ahead.
- Chris Keller:** Thank you for that. Most of my clinical questions have been answered, but Megan, just on the commercial side, can you maybe put into perspective, what does this result mean in terms of a timeline in terms of moving into phase three and how's the company funded for that?



- Megan Baldwin:** Right. So we're in a really strong cash position as we said in the announcement. By the end of the year we should have in the order of 30 million Australian dollars cash-in-bank. That is sufficient for us, obviously, to read out our Phase 2A DME clinical trial. We have sufficient cash over the next 12-18 months as we are also able to do preparatory planning work for the phase three. We would also be looking at all of the other strategic options in order to be able to take this through into a phase three programme.
- We'll obviously keep the market updated now that we've reported out.
- Chris Keller:** Thanks for that, Megan. Just lastly in terms of the overall commercial strategy for this programme. Are you looking to licence out and if so, what stage would be best?
- Megan Baldwin:** Yes, that's a good question. Obviously on the back of the data, we'll look at all of the options that are available, licencing partnership, taking it forward ourselves. All of those options are on the table. We're not in a position at this point in time to have anything more, other than the fact that on the back of really good data, we have multiple options available to the company and I think this is going to really be exciting for a lot of corporates out there. A lot of companies that are already in the space, but also for the benefit of patients. The most important thing is that this is a drug that's moved forward into a phase three registrational programme and that's how we'll approach it.
- Chris Keller:** All right. Thanks again for that. Good to have some good news on the biotech front. Thanks.
- Megan Baldwin:** Thanks very much.
- Operator:** Thank you. Your next question comes from Ben Rosenfield. Please go ahead.
- Ben Rosenfield:** Oh, good morning. It's Ben. How are you?
- Megan Baldwin:** Thanks.
- Ben Rosenfield:** This summer ... I live in Queensland. Just from a patient's perspective, I've just been following your reports for the last six months. I haven't bought any stock but I'm around like 50 is there any ... if you just went to your local GP and ask the question, how do I get these types of injections to reduce [inaudible] so my vision doesn't get worse. Is this, are these studies covering just reading vision or long distance vision as well?
- Megan Baldwin:** Well, specifically this particular trial and this drug now is in development for wet AMD as well as diabetic macular edema and we do have Australian sites opened for the diabetic macular oedema trial. With that, that's a conversation you'd have with your ophthalmologist in order to know if they are participating in any particular studies and if of course your disease was appropriate for each individual clinical trial that they might be involved in.
- Ben Rosenfield:** Yeah. I don't have a medical background, but would you go to a GP or-



**Megan Baldwin:** Oh, you probably need a referral to start, start with your GP and ask for a referral would be my recommendation there.

**Ben Rosenfield:** Because it got mentioned in the beginning of the conference that it can prevent vision loss if it's sort of minimal, say in the early stages or there's no vision loss at all. Can you take, can you get these injections to prevent any type of loss?

**Megan Baldwin:** Pravin, would you like to just very briefly just comment on that one?

**Pravin Dugel:** Well you know, this is for a specific disease which is a devastating consequence of macular degeneration from ageing process, so I wouldn't just categorise it as vision loss because there can be a whole bunch of different things that cause it. But to Megan's point, this is something that you would go to a general ophthalmologist or an optometrist and they would then be able to diagnose and refer properly.

**Ben Rosenfield:** Yeah. Okay. Thank you.

**Megan Baldwin:** Thanks very much.

**Operator:** Thank you. Your next question comes from Mark Pachacz from Bioshares. Please go ahead.

**Mark Pachacz:** Hello, Megan. Well done on the results. This is a question for the clinicians. I'm just wondering how this sort of improvement might change with compliance with VEGF-A style or VEGF-C drugs. I'm just wondering at which point do patients stop getting therapy because of, perhaps, they're not seeing enough of a benefit to warrant the monthly injections and how this sort of a change might impact the of the compliance there?

**Pravin Dugel:** Yes, so this is Pravin I would say if you look at some of the studies that have been done in the US, and I can point to one study that has been done from Scott Cousins, there is a alarming and astonishing delta between clinical trials and real life outcomes. About 50% of patients simply don't come back for treatment, and a lot of that is due to the fact that they simply don't see the kind of improvement that they want to see. When I said the examples earlier on this phone, you know, I can't drive. I still can't see my textbook. I still can't read my emails. And there's no doubt in my mind whatsoever that seeing patients on a daily basis in a week with a clinician that a lot of that is because of that unmet need of improved efficacy. And clearly durability has something to do with it to, but we'll talk about that in just a bit.

So my first point is, if you can go ahead and improve efficacy, there's no doubt in my mind whatsoever that you will increase compliance. If somebody comes in and says, "you know, because with this drug that I'm taking, even if it's every four weeks, I can now drive and I can now go ahead and live independently and I don't have to be in a home." There's no doubt that that will increase compliance. That's the compliance. That's the compliance and efficacy part. However, remember this trial that you're seeing now was designed towards safety and efficacy. You don't know what we'll do in durability. And to me it makes intuitive sense that



if you have a drug that increases efficacy, we will also increase durability. And intuitively that makes sense.

Again, this is an extrapolation that I'm making from a scientific point of view. That wasn't the purpose of those studies. But I look at this and say, look, if the drug has a different mechanism whereby it gives me more efficacy and better affects this pathology, then there's a very good chance that I'll have to treat fewer patients for a lesser period of time.

And that also certainly will increase compliance. So improving efficacy is the primary unmet need, but the highest bar by far. Increased durability is also an unmet need, but they're not separate. They go hand in hand. So again, that's not what this trial was designed to do. Most trials are designed to go over the lowest bar. And the lowest bar, which is still important, is increased durability. This trial was designed to go above the highest bar, which is increased efficacy. And that bar has been a key, and I think that over time there's been more studies that will be done that will show an increased durability. But even if that's not the case, just the concept is increased efficacy will certainly improve compliance. There's no doubt in my mind.

**Megan Baldwin:** Just, Tim, a couple of concluding remarks on that point before we finish up?

**Tim Jackson:** Yeah, I think a very central person said to me once that basically the efficacy trumps durability and that's exactly what Pravin's just said. I think if we improve efficacy, that will be what matters. I think the other interesting thing is that the remarkable thing about this is getting such a good result, a positive result, a significant results against an amazing, plus 10 letters in the Lucentis arm. And in the real world we're not going to be seeing 10 letters going into Lucentis. So I think if anything the struggle in the real world will actually push up that Delta significantly because the patients are going to be getting five or six letter gains with Lucentis which gives you much more room to add to the visual gains with a second agent. My suspicion is if this was rolled out, we'd see a much bigger impact in the real world and as Pravin says that will drive compliance.

**Megan Baldwin:** Okay. Thank you. I think at this point, thank you very much for those comments, Tim and Pravin. I would like to just make some concluding remarks. Firstly, thank you to the operator and really thank you everyone for joining today's teleconference.

Before concluding the call on behalf of the management team at Opthea, I sincerely wish to express our gratitude to the patients, the investigators, and the site staff who participated in this study. I also wish to extend our appreciation to our longstanding shareholders for their continued support and shared vision for the development of OPT-302.

Moving forward, we will continue to analyse the data that we've generated in the phase 2B trial and we plan to present that in detail at an upcoming ophthalmology meeting.

Please bear in mind that we do anticipate reporting top line data from our phase 2A clinical trial in patients with persistent DME. This is anticipated in early 2020. All of us at Opthea are



very excited for the journey ahead for both the wet AMD and DME programmes, and I'll certainly keep everyone updated. In the meantime, please don't hesitate to get in touch with me directly with any follow-up questions, and thanks again for participating in today's call.

**[END OF TRANSCRIPT]**