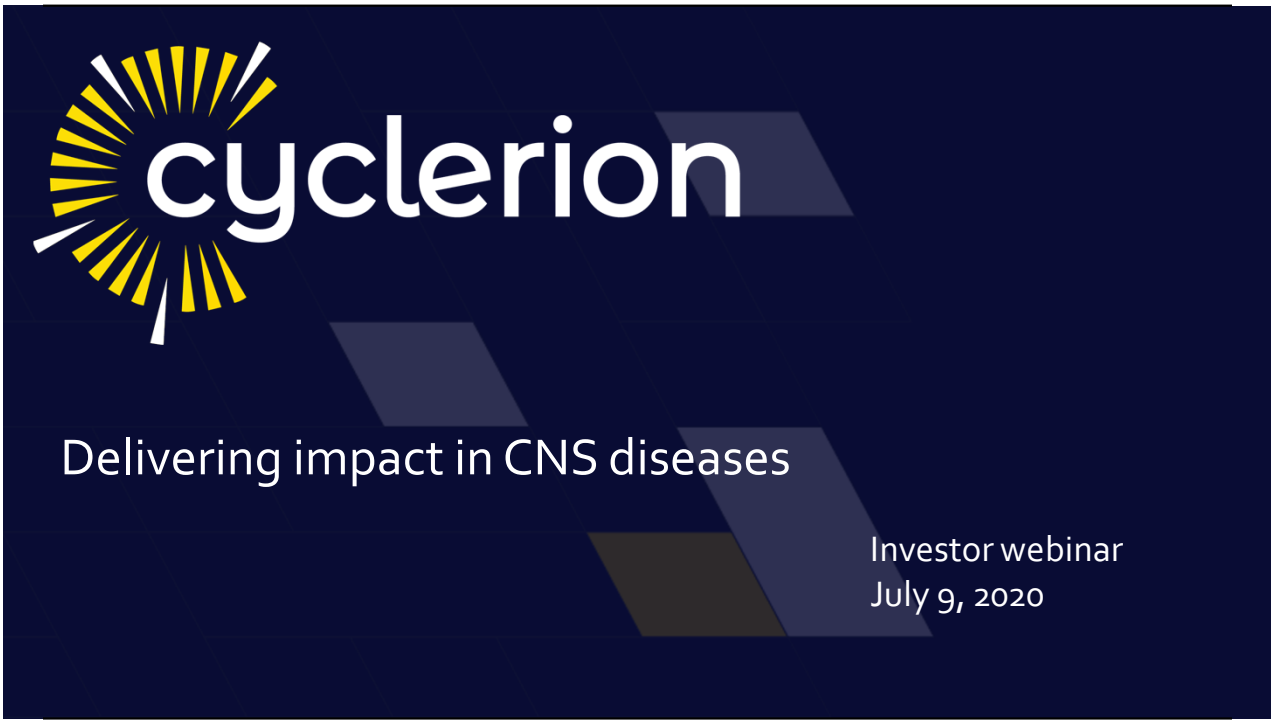



**Peter Hecht (00:00:04):**
Okay, great. Let's get started. Good morning. Welcome to our CNS Focused Investor event. We're pleased to have you join us. Today's webinar is going to be centered on IW-6463, our oral once daily, CNS penetrant sGC stimulator. We want to tell you why we're so excited about its drug attributes and its therapeutic potential. And we want to take a dive into the initial indications that we've selected to explore its full potential. And, we'd like to describe to you the adaptive and learning approach that we're taking to development of this molecule. Next slide, please.

## Safe Harbor Statement

This presentation contains forward-looking statements. Any statements contained in this presentation that are not historical facts may be deemed to be forward looking statements. Words such as "anticipate," "believe," "potential," "expect," "may," "will," "should," "could," "plan," "estimate," "target," "project," "contemplate," "intend," "future," "will," "predict," "continue," and the negative of these terms and similar expressions are intended to identify these forward-looking statements.

These forward-looking statements are based on Cyclerion's current expectations, projections and trends, are only predictions and involve known and unknown risks and uncertainties that could cause actual results to differ materially from those expressed or implied in such statements. Investors are cautioned not to place undue reliance on these forward-looking statements, which include but are not limited to statements about possible or assumed future results of operations; preclinical, clinical and non-clinical studies, the interpretation of data therefrom and the ability to replicate findings from such studies; business strategies, research and development plans, collaborations, partnerships, out-licensing (including without limitation with respect to praliciguat), regulatory activities and any timing thereof; competitive position, potential growth or commercial opportunities; the clinical potential, application, commercialization or potential markets of or for any proposed products; the anticipated timing of release of data from any clinical trials; and the size and design of those clinical trials.

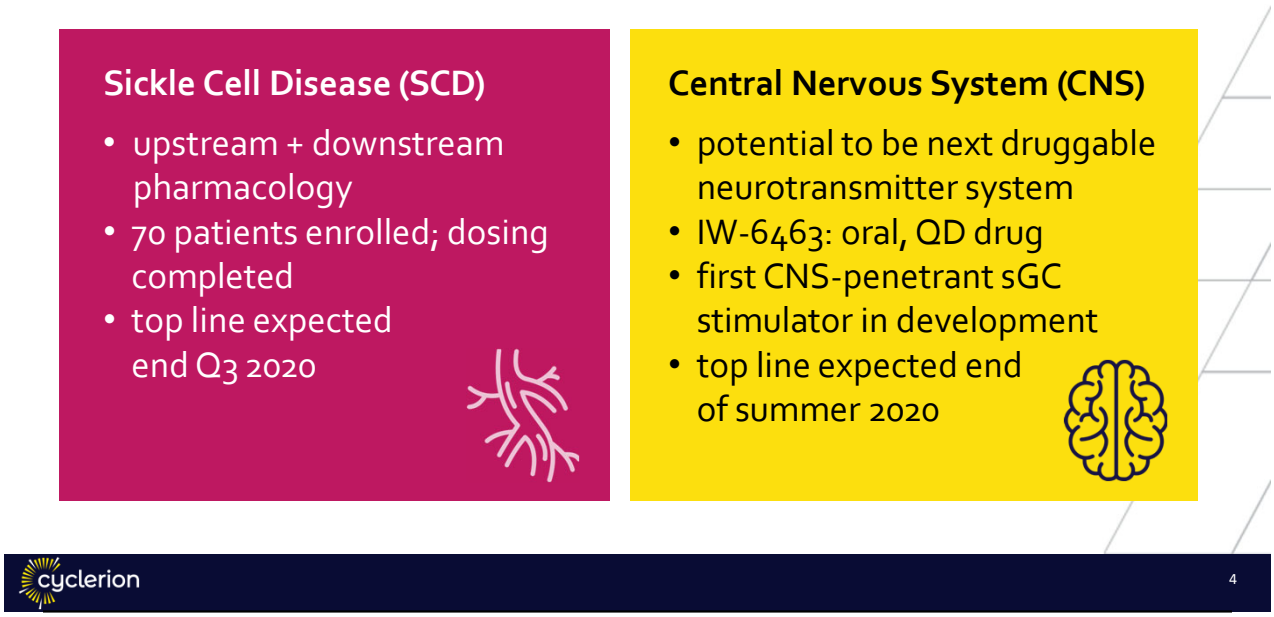
Applicable risks and uncertainties include those listed under the heading "Risk Factors" and elsewhere in our most recent Form 10-K filed with the SEC on March 12, 2020, and in our subsequent SEC filings, including our Quarterly Report on Form 10-Q filed with the SEC on May 4, 2020. These forward-looking statements speak only as of the date of this presentation, and we undertake no obligation and do not intend to update these forward-looking statements.



**Peter Hecht:**
We're going to be making forward looking statements during the course of this discussion. You can read our full Safe Harbor statement by accessing this presentation along with recent press releases on our website.

**Peter Hecht (00:00:58):**

I'm Peter Hecht, I'm the CEO and I'll be your host for today. I'm joined by several of my colleagues, including members of the management team and our CNS program team. Given the short time together, we're not going to have introductions and have people describe their bios, but all of the bios are available on our corporate website. We're especially pleased and honored today to have two outside clinical specialists join us and share their perspective on the two diseases we're tackling. Dr. Marni Falk and Dr. Eric Smith. Dr. Falk and Smith will each spend some time talking about the patients, the unmet clinical needs, and the opportunity for new therapeutics in these first CNS indications. We thank them for making the time to join us today to share their perspective. With that, I'd like to turn it over to Cheryl Gault, our Head of Strategy and Corporate Development to introduce you to the program. Thanks. Cheryl.




**Cheryl Gault (00:01:57):**

Great. Thank you, Peter. Cyclerion is a clinical stage biotech company, pioneering the advancement of sGC stimulators in two important therapeutic areas, sickle cell disease and CNS. In sickle cell disease, we have an ongoing phase two study investigating our sGC stimulator, olinciguat, and are very excited to announce that enrollment has closed with 70 patients and dosing has been completed. Our program team was relentless in driving both enrollment and follow up in this important study despite the challenges presented by COVID-19. We expect to release top line data for this study in late Q3. Sickle cell disease is a debilitating multisystem disease and patients need a comprehensive treatment. We're very pleased to see two new treatments enter this market. These are important advances for sure and their positive receptivity is really encouraging.

**Cheryl Gault (00:02:50):**

We also believe that there continues to be significant unmet need in sickle cell disease, and that there's plenty of room in this market for more innovation. This is why we're excited to learn more about the clinical profile of olinciguat from our ongoing study. Given the broad pharmacology of sGC stimulators, we anticipate an efficacious and differentiated profile that will add meaningful new clinical benefit for patients with sickle cell disease, either alone or in combination with existing treatments. We expect to have additional investor events for our sickle cell program once the data from the ongoing phase two study are available.

**Cheryl Gault (00:03:26):**

The purpose of this call is to focus on our CNS program, which is the part of our story which is perhaps less well known, but it's certainly no less exciting. As leading experts in the field of sGC, we are advancing the first sGC stimulator to cross the blood brain barrier. And we believe that this mechanism has the potential to create the next big breakthrough in CNS by stimulating a previously undrugged neurotransmitter system. Other successfully drug neurotransmitter systems, for example, the

dopaminergic or the cholinergic systems opened up entirely new therapeutic categories and created significant market opportunities as a result. This kind of therapeutic potential opens tremendous opportunity to help a wide range of patients suffering from CNS diseases. It also makes our CNS program an exciting part of our strategic focus today, and a core part of Cyclerion going forward. Next slide, please.

## Cyclerion: delivering impact in CNS

| | |
|---|---|
| 1 | Now is the time: value in CNS |
| 2 | sGC and CNS: scientific and clinical basis for CNS therapies |
| 3 | Translational pharmacology study: demonstrating CNS activity |
| 4 | Clinical direction in CNS: important indications that yield early answers |

**Cheryl Gault (00:04:20):**

During our time together today, our discussion will center around the following themes. Now is the right time for sGC and the CNS, the increase understanding of patient and pathway biology has increased our confidence. There is a strong, scientific and clinical basis for the application of sGC in CNS indications, which we will share. Our translational pharmacology study is an important upcoming data set where we expect to demonstrate CNS activity. And lastly, the clinical direction of our program in CNS and how we are thoughtfully picking clinical indications and designing efficient early clinical studies. Next slide, please.

## Objectives for today

| | | | |
|---|---|---|---|
| 1 | Now is the time: value in CNS | | **How Cyclerion can create value in CNS** |
| 2 | sGC and CNS: scientific and clinical basis for CNS therapies | | **Discuss the broad therapeutic potential of sGC stimulators in CNS** |
| 3 | Translational pharmacology study: demonstrating CNS activity | | **Describe the rich yield of data and its implications (data due late summer)** |
| 4 | Clinical direction in CNS: important indications that yield early answers | | **Discuss our first indications: focused patient populations, biomarker-based development** |

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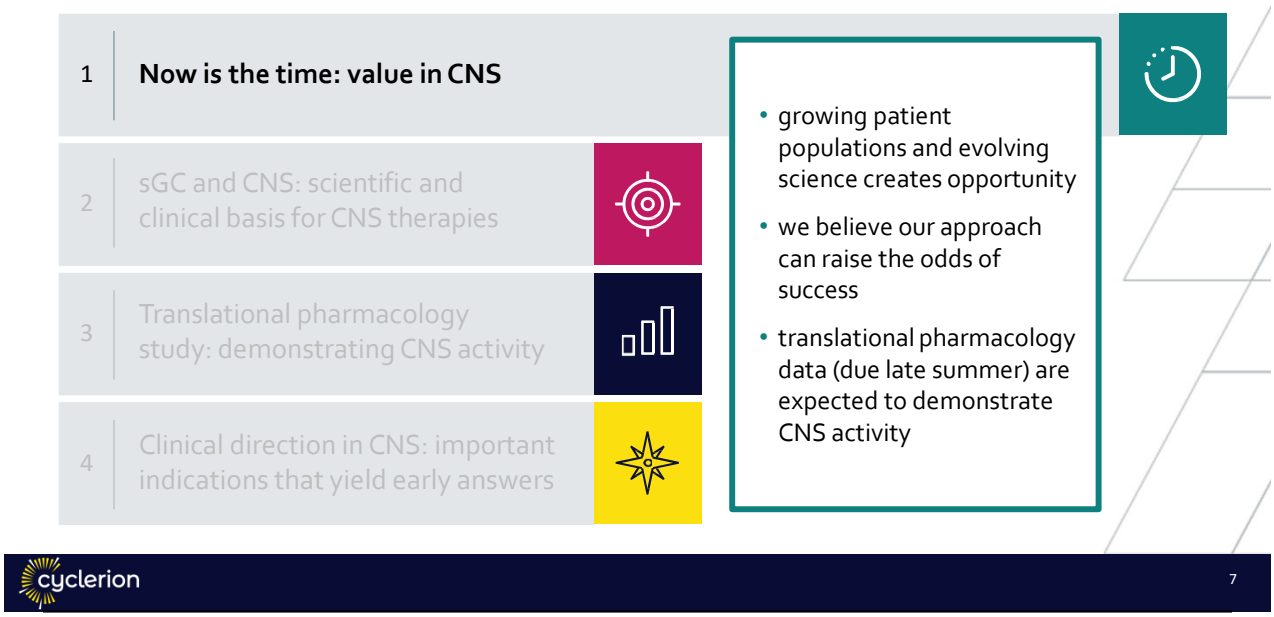
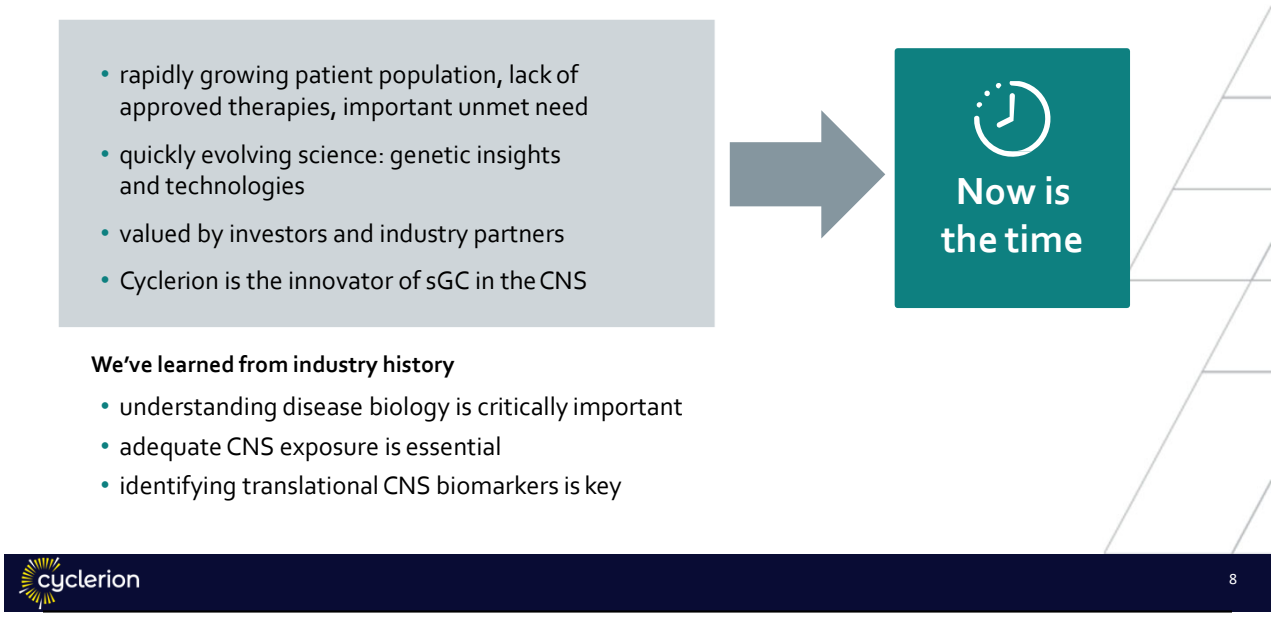
**Cheryl Gault (00:05:01):**

For each of these themes, we have a specific objective for the call today and what we hope you get from our time together. By the end of the call, we hope that you have a clear picture of how we intend to create value in the CNS, an exciting yet complex therapeutic area. The broad therapeutic potential of sGC stimulators in the CNS. This is by virtue of the multidimensional pharmacology that can be achieved by stimulating this untapped neurotransmitter system. What we expect from the upcoming results in our translational pharmacology data, and lastly, our development approach and why we are so excited about the opportunities and the first two focus patient populations we intend to pursue. Next slide, please.




**Cheryl Gault (00:05:41):**

Let's start with now is the time. Rapidly evolving, scientific understanding of disease and pathway biology and the CNS makes for a big opportunity for new drugs. We are focusing on understanding the intersection between patient biology and pathway biology to raise the odds of clinical success. We have important clinical data coming in late summer, which will help inform future development. Next slide.



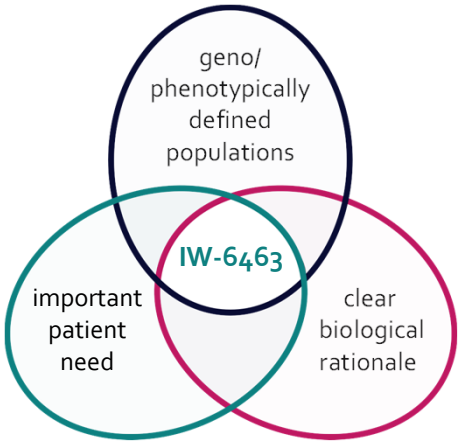

**Cheryl Gault:**

So here, just a few comments on how we think about capturing potential in the high reward therapeutic area that is the CNS. There is no doubt that CNS is a high reward space where the unmet needs are huge given the rapidly growing patient populations and the dearth of approved and effective treatments. Any mechanism that provides real clinical efficacy is going to be very valuable clinically and commercially, and the rapidly evolving science, both genetic insights and technologies, is making new drugs more tangible.

**Cheryl Gault (00:06:40):**

This dynamic creates a lot of interests from both investors, as well as industry partners. Those who are looking to add novel treatments to build their portfolios in CNS. And we are the innovators here. We have the first CNS penetrant sGC stimulator advancing forward in CNS diseases. We also appreciate history. We're learning from the programs that have come before us in the CNS and are applying those learnings to our program. Specifically, that it's imperative that we continuously work to increase the understanding of the disease biology in order to effectively identify the right patients to study, that we're getting adequate CNS exposure to have a pharmacologic effect, and that we're investing early in the development of biomarkers that can help to translate our scientific understanding into the clinic and can guide future clinical development. This is a very exciting time to be in CNS drug development. The scientific landscape is rapidly evolving, and if we have a drug that really works for patients, we know we'll be making a difference in the lives of many and building a core CNS franchise in the process. Next slide please.

## Our approach: intersection of patients and biology




**Raising the odds of success:**

- pursue multiple indications in parallel
- leverage biomarkers to drive development
- implement nimble trials with leading edge investigators and imaging analytics
- investigate a strategic R&D partnership to explore full potential of sGC in the CNS

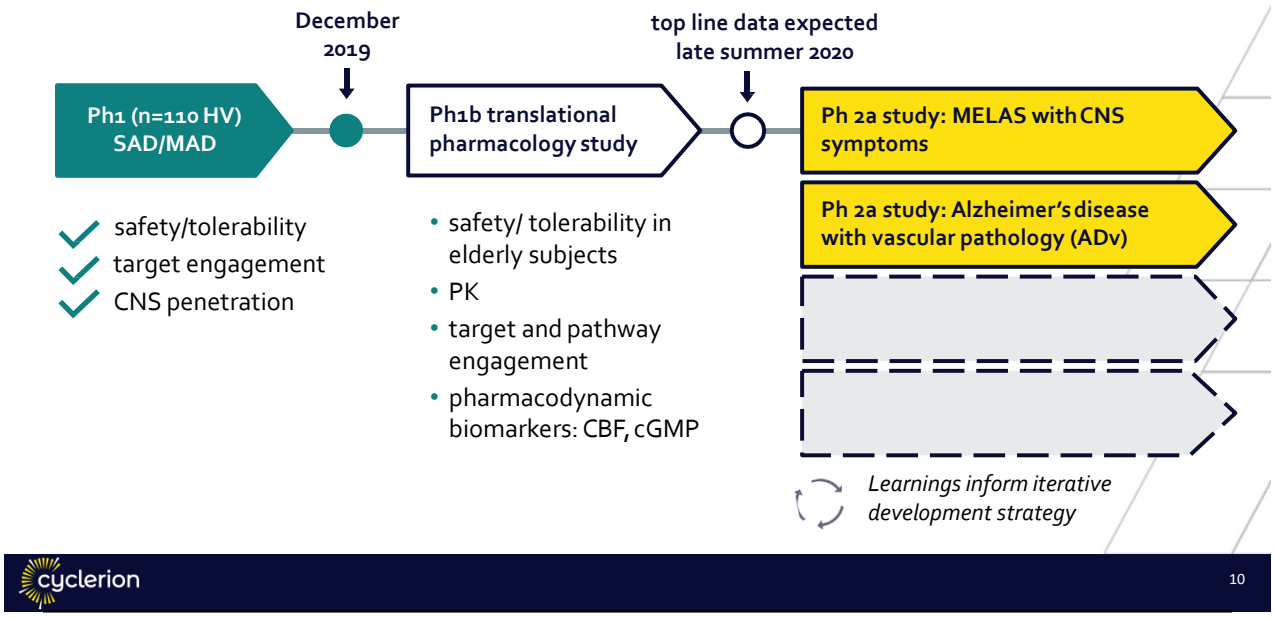


**Cheryl Gault (00:07:45):**

So I think the question is, how do we raise our odds of success in the CNS? Well, our approach is to focus on the intersection of three things. Important unmet patient need where a new treatment will be clinically valuable, sound biological rationale for the application of the sGC pathway, and selecting genetic and phenotypically defined patient populations where we can reduce variability. We believe that in focusing on the intersection of these three things, we're pointing our mechanism at the indications where it's most likely to have the biggest impact and therefore, give us the best chance to detect a signal in early clinical studies. Beyond indication and patient selection, the other ways that we believe we can raise the odds of success are pursuing multiple indications in parallel, which is critical to driving both near and midterm value, leveraging a biomarker based development strategy, whereby clear results are de-risking for future studies, and designing small nimble studies that take advantage of the latest brain imaging analytics.

**Cheryl Gault (00:08:48):**

Lastly, we're exploring an R&D collaboration in order to support the development of more indications in parallel. A great partner can bring expertise and capabilities and help us increase the total investment that can be deployed against what we see as a really big opportunity in the CNS. Next slide, please.

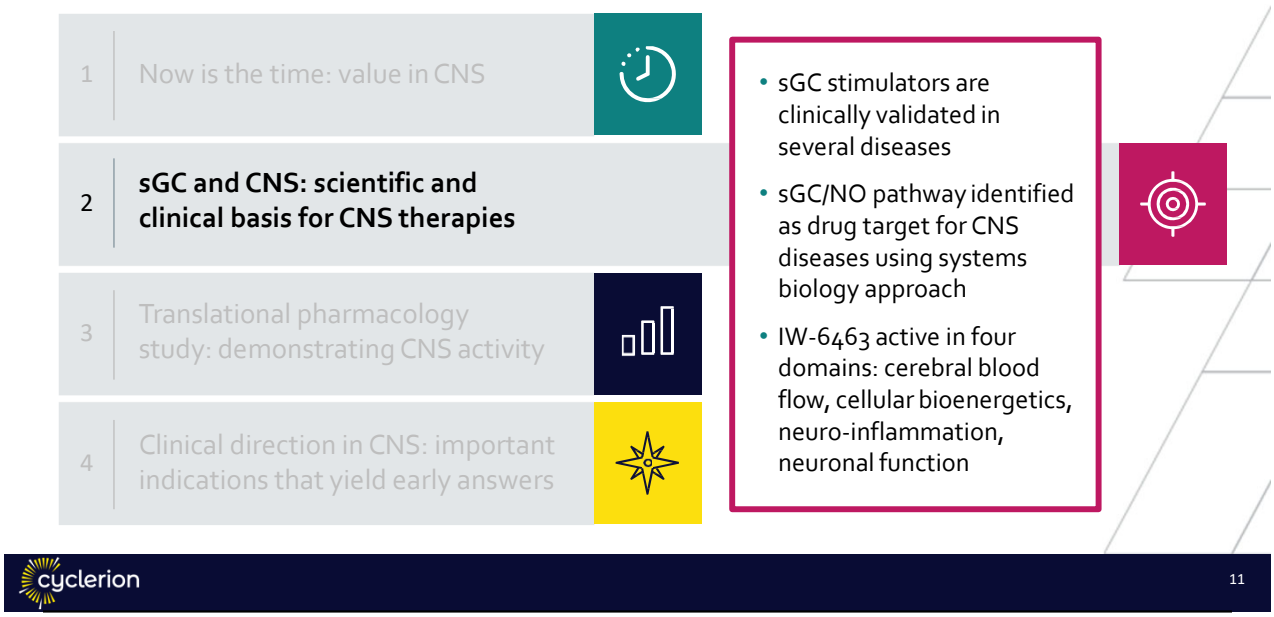



**Cheryl Gault (00:08:48):**

So this page gives you a bit of a roadmap, if you will, of where we are and where we're going. IW-6463, our CNS penetrant sGC stimulator, has completed phase one and the results there were very encouraging. We then initiated a translational pharmacology study in elderly subjects, and this is a study that will allow us to demonstrate that the biomarkers that moved in our preclinical work can be translated to humans, thereby enhancing our confidence as we move forward in the clinic. We expect these results in late summer.

**Cheryl Gault (00:09:38):**

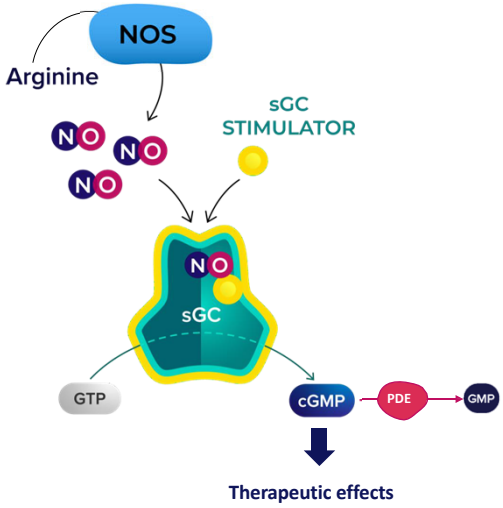
The next step of course, is moving into patients and we have plans to move IW-6463 forward in two indications to start: MELAS, which is a rare mitochondrial disease, and Alzheimer's disease with vascular pathology, which we call ADv for short. This is an identifiable subset of mixed dementia patients. Both of these initial indications have a compelling scientific rationale. And for both, we have selected a defined and identifiable patient population, and a patient population where we can apply a biomarker based development plan. You'll hear much more detail about these indications in the clinical section to follow. But first, I'd like to turn the call over to Drs. Mark Currie and Andy Busch to talk about the scientific underpinnings of our CNS program. Mark.




**Mark Currie (00:10:28):**

Good morning, everyone. Thanks, Cheryl. And thank for you who are participating on this event. sGC, is a clinically validated target. The pathway had many successful drugs. Most recently with the sGC stimulators, there's clear evidence that this pathway, this approach can be utilized to deliver meaningful therapeutic options for patient. The pathway in the CNS is evolving and we're learning a great deal. It's very clear this system is expressed, highly expressed throughout the CNS. When we take a systems approach and pathway mapping, we see very clear evidence that this pathway is critical to basic neuronal functions and also has a role in neuro pathophysiology. IW-6463 represents a clear breakthrough. It's the first sGC stimulator that crosses the blood brain barrier. We'll show you that it has activity in at least four key domains, and we'll go into more detail around these domains. But to set it up at the beginning here, what we see is clear evidence of improvements in cerebral blood flow, cellular bio energetics, we see decreases in neuro-inflammation and improvement in neuronal function. Next slide, please.

## sGC stimulators: ideal intervention in a genetically and clinically validated pathway




**Multiple successful drugs target the NO-sGC-cGMP pathway for the treatment of CV diseases**
NO donors, PDE5 inhibitors, sGC stimulators

**NO-sGC-cGMP pathway plays central role in CNS diseases**
Network analysis delivers z-scores for CNS diseases similar to validated CV diseases

**sGC: optimal target for pathway intervention**
Broadly expressed in CNS, amplifies endogenous signaling, increases cGMP levels at the source with no attenuation of response

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**Mark Currie (00:12:00):**

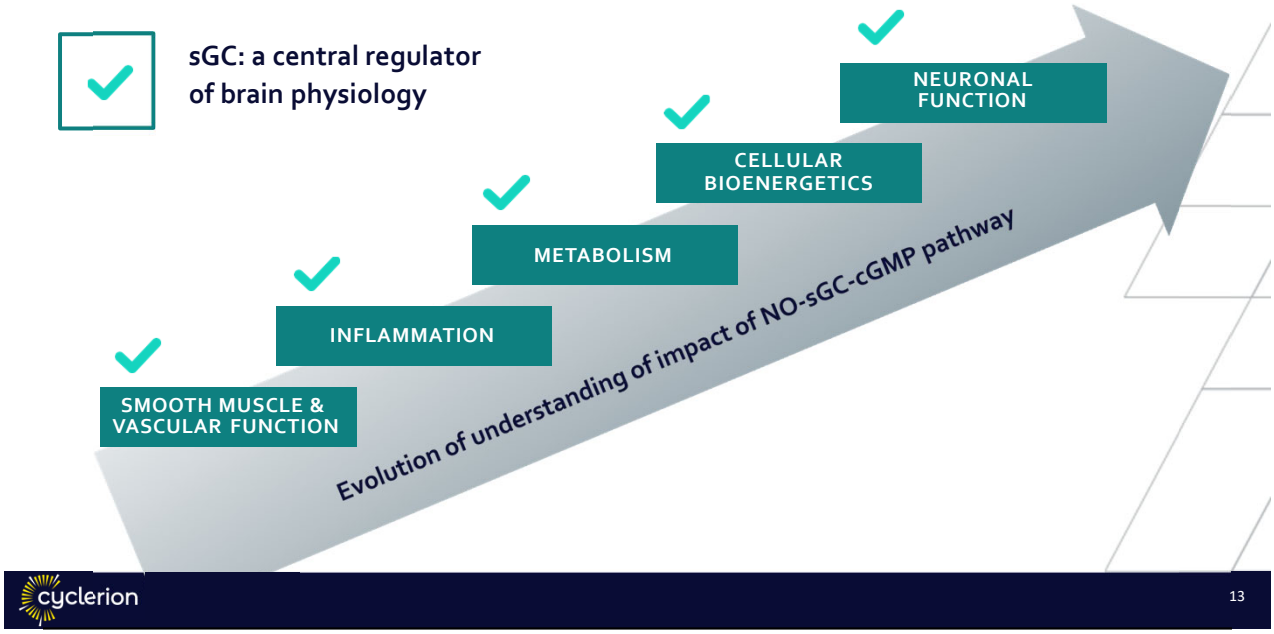
So when you look at this pathway, I would start with the regulation of the pathway. Arginine is converted by the enzyme, nitric oxide synthase. This enzyme then convert so that you produce nitric oxide endogenously. It then activates this nitric oxide, then activates the soluble guanylate cyclase as a stimulator. This causes the conversion of GTP to cyclic GMP. And what we see with this effect of the endogenous nitric oxide, we can potentiate that effect with an sGC stimulator so that you get this even more increase of cyclic GMP, but it's in alliance with the endogenous system. It's boosting the endogenous system.

**Mark Currie (00:12:50):**

This pathway has been a source of multiple breakthrough drugs over many decades and years for advancing drugs. Nitric oxide donors go back over a hundred years, nitroglycerin being used for angina treatment and other cardiovascular disorders. More recently, PDE5 inhibitors came forward for erectile dysfunction, BPH, and PAH. And then even more recently the first sGC stimulator was advanced by my colleague, Andy Busch, that we see the utility of this pathway, of this approach for treatment of PAH and there are further indications and other cardiovascular diseases. The nitric oxide system is critical and it plays a central role in CNS diseases. We've done a great deal of pathway mapping and network analysis for examining the role in CNS diseases, and we'll go into detail, but obviously we believe that Alzheimer's disease with vascular pathology and MELAS represent two of the exciting potential areas we may be able to help patients with this approach. sGC is optimal for boosting this pathway in the CNS.

**Mark Currie (00:14:13):**

As we said before, it amplifies the endogenous signaling, increasing the cyclic GMP levels for a longer period of time and higher concentration. And also there's no attenuation of the response as you see with NO donors. Next slide, please.




**Mark Currie:**

Examining this broad rich effects of the sGC stimulators in the CNS, and then also this pathway and what it's doing in the central nervous system goes to a number of fundamental activities. What we see is that we can enhance cerebral vascular, smooth muscle function, and vascular function. We can increase cerebral blood flow in localized areas that matches through the energetic needs of the brain. We also see decreased vascular inflammation and improvement in the blood brain barrier so that we decrease increases in permeability.

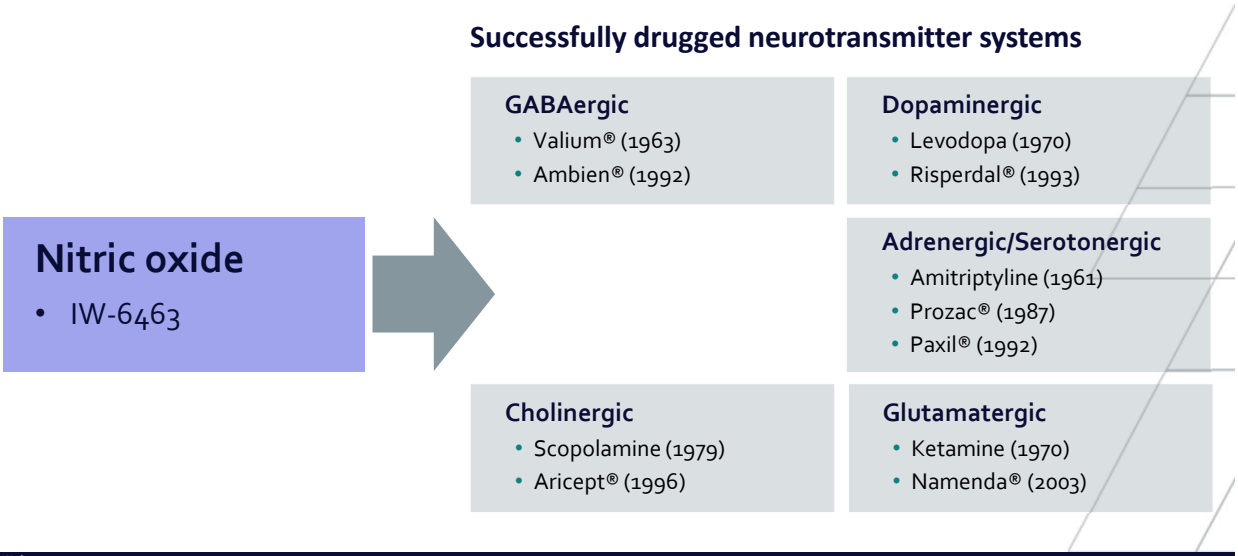
**Mark Currie (00:15:22):**

Also, we see this pathway as anti-inflammatory, so it blocks the inflammation that is occurring in the vasculature, and also in monocytic cell lines, so we see a reduction of pro-inflammatory cytokines in the brain. And then if you look at the effects on metabolism and these effects are broadly across the systemic effect, what you see is we decrease glucose levels in diabetic animal models that we've examined, but also when we've looked at diabetic patients, and we see also reduction in lipids, in particular LDL cholesterol. When you also then go and further examine what this pathway activity may be able to generate, we see improvements in cellular bioenergetics, including improvements in mitochondrial function and cell lines from patients that have mitochondrial diseases, we can improve the production of ATP, and it's evident that this system stimulates mitochondrial biogenesis.

**Mark Currie (00:16:33):**

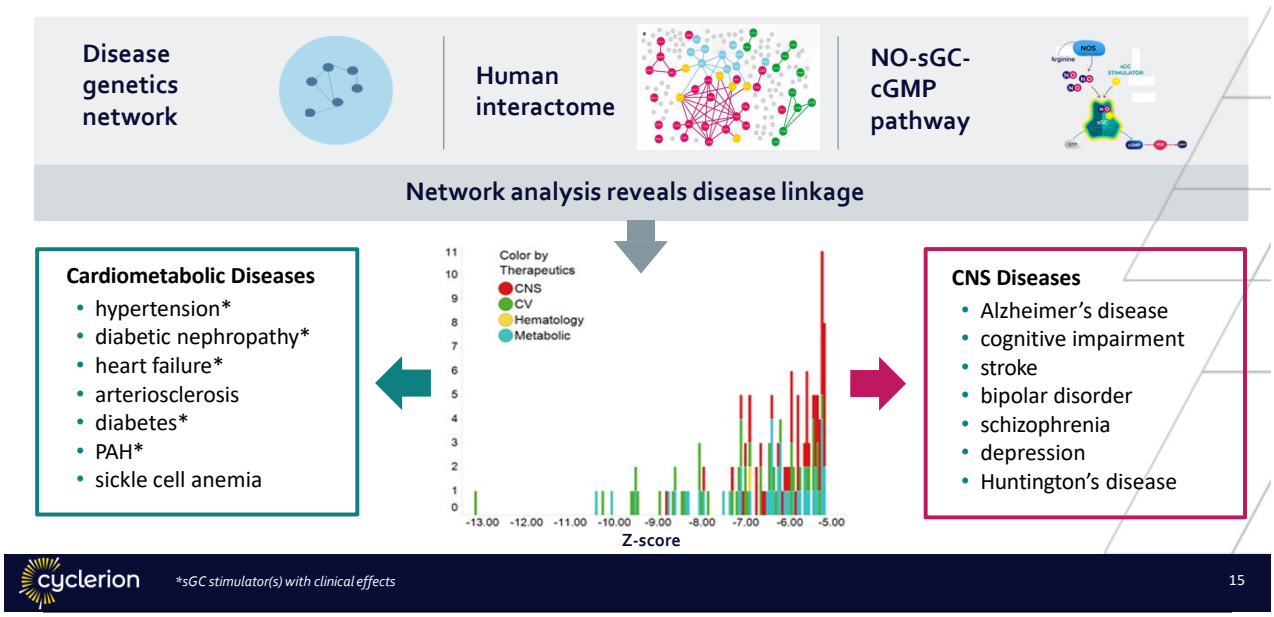
Also, excitingly, this system acts directly on neuronal function. Nitric oxide is a neurotransmitter, well-defined, and so we're boosting the activities with an sGC stimulator of the nitric oxide neurotransmitter function, which is often centered around improvements in cognition, memory and executive function and alertness. All of these broad pharmacologic effects are critical in our sense of thinking through potentially improving the lives of patients that have MELAS and also Alzheimer's disease with vascular pathology, and ultimately, we think in a number of other potential CNS diseases. Next slide, please.

## sGC stimulators: potential to be next druggable neurotransmitter system




**Mark Currie (00:17:26):**

With that, I'd like to also just end with a pretty exciting concept that nitric oxide is the next big area for a direct effect on a neurotransmitter system. Drugs that have been highly successful, drug classes and multiple drugs inside them, are potentially having effect on CNS function. As we well know, I've shown in this slide the multiple classes, as an example, the SSRIs for treating depression and mood disorders made a major advance, and we think nitric oxide has this role in neurotransmission and ultimately, sGC stimulators with IW-6463 being the first in class, have that potential also to bring forward really important drug class. The innovation at the beginning of an innovation with IW-6463, and we expect future drugs in this class also to help patients. So with that, I'll turn the presentation over to Andy Busch and Andy is our Chief Innovation Officer.

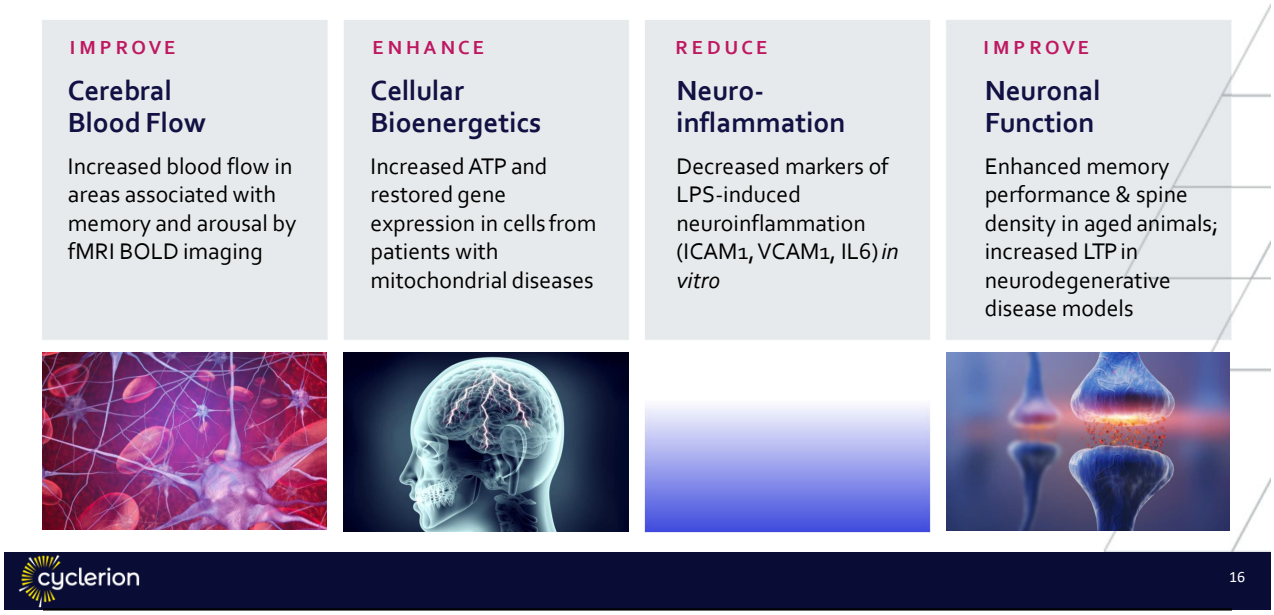



**Andy Busch (00:18:46):**

Thank you very much, Mark. I think Mark nicely laid out the groundwork and the ideas of the importance of the NO-sGC cyclic GMP pathway. I think it is very clear from the description you've heard that this pathway is a validated pathway in a number of cardiometabolic diseases. Going towards a difficult area, such as the CNS, it was of utmost importance for us to really validate this pathway to the best we can for diseases of the CNS. For that purpose, we did a network analysis, which we utilize to disease linkage the pathway to our genetics network, to the human interactome, back to several drug pathways.

**Andy Busch (00:19:49):**

Doing that, and analyzing over 20 databases across the platforms described at the top, we came to the result, first of all, that this is a validated approach because what we found was indeed cardiometabolic diseases, which were the ones where different types of sGC stimulators were shown in the past to produce beneficial effects such as diabetic nephropathy, heart failure, or pulmonary hypertension. But we also saw with a very high significance popping up several CNS diseases. Some of those listed on the right. This gives us comfort that indeed we can link the pathway by means of human interactome and genetics to CNS diseases. With that, we employed of course, a battery of preclinical experiments to see effects of our brain permeable compound IW-6463 on hallmarks of neurodegeneration. And you see that on the next slide.




**Andy Busch (00:21:10):**

What you can see here is the summary of experiments we have performed to test for effects of our compound on cerebral blood flow, cellular bioenergetics, neuro-inflammation, and neuronal function. What we found on cerebral blood flow was indeed in rat brain, an increased blood flow, an increased blood flow in the area where we believe it is important for a number of neurodegenerative side effects. So we do find indeed an increased blood flow in the hippocampus, in the thalamus, or in the reticular activating system, and believe that this increased blood flow is of significant benefit in these areas. Cellular bioenergetics, we do see indeed in cells of Leigh's syndrome patients, patients with mitochondrial disease and increased ATP production, and we also see a restored gene expression in cells from those patients because we find a nicely increased TFAM expression increase, which is important for mitochondrial increase of gene expression.

**Andy Busch (00:22:35):**

On neuro-inflammation, we see both in rat as well as in mouse models an impact on LPS induced neuro-inflammation. We can see that indeed we can decrease with a compound inflammation markers, such as ICAM1, VCAM1, and IL6 both in mouse and rat models and different cell types. Finally, we can also show that we improve neuronal function both in experiments testing the function, as well as the tissue composition. We can see an enhanced memory performance, and we can see an increase in spine density in aged animals, and indeed those aged animals from the structure of their spines, looked like young animals after treatment with 6463. We also could show an increase of long-term potentiation in neurodegenerative disease models. Next slide.

## Attractive nonclinical profile supports clinical development

- IW-6463 demonstrates pharmacological activity across four distinct domains in multiple preclinical models
- preclinical results support straightforward translation into the clinic
- CNS exposure and target engagement demonstrated in multiple species
- no evidence of CYP enzyme inhibition and IW-6463 not a P-gp substrate
- nonclinical toxicology profile consistent with other sGC stimulators in development

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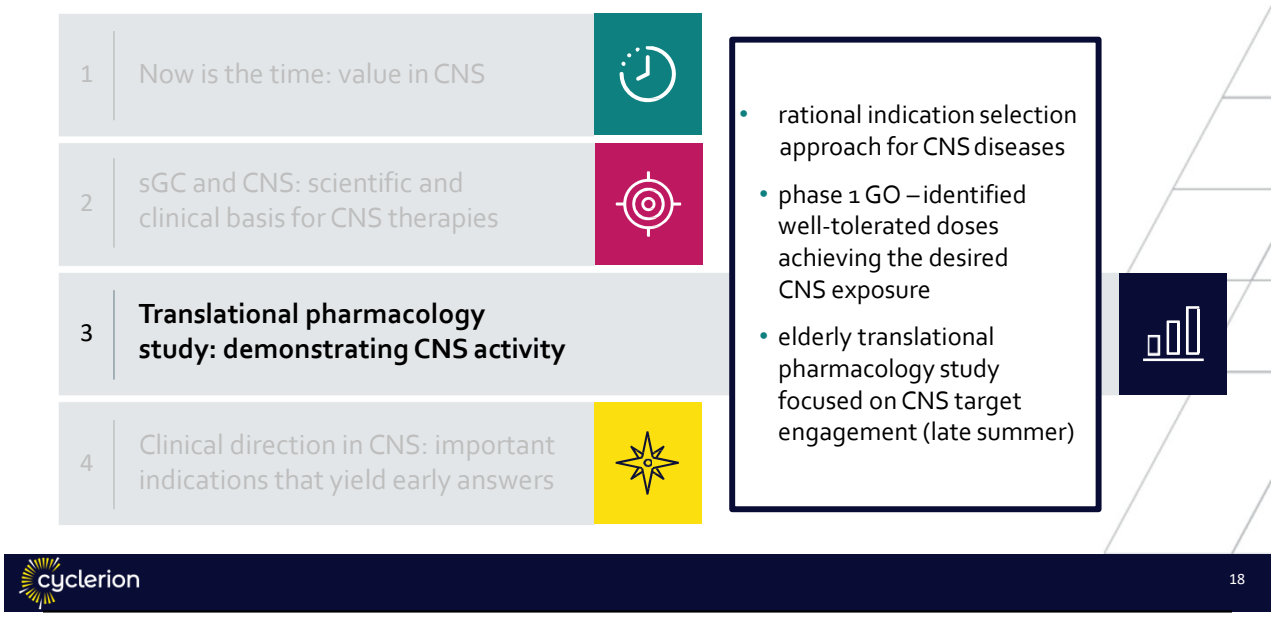
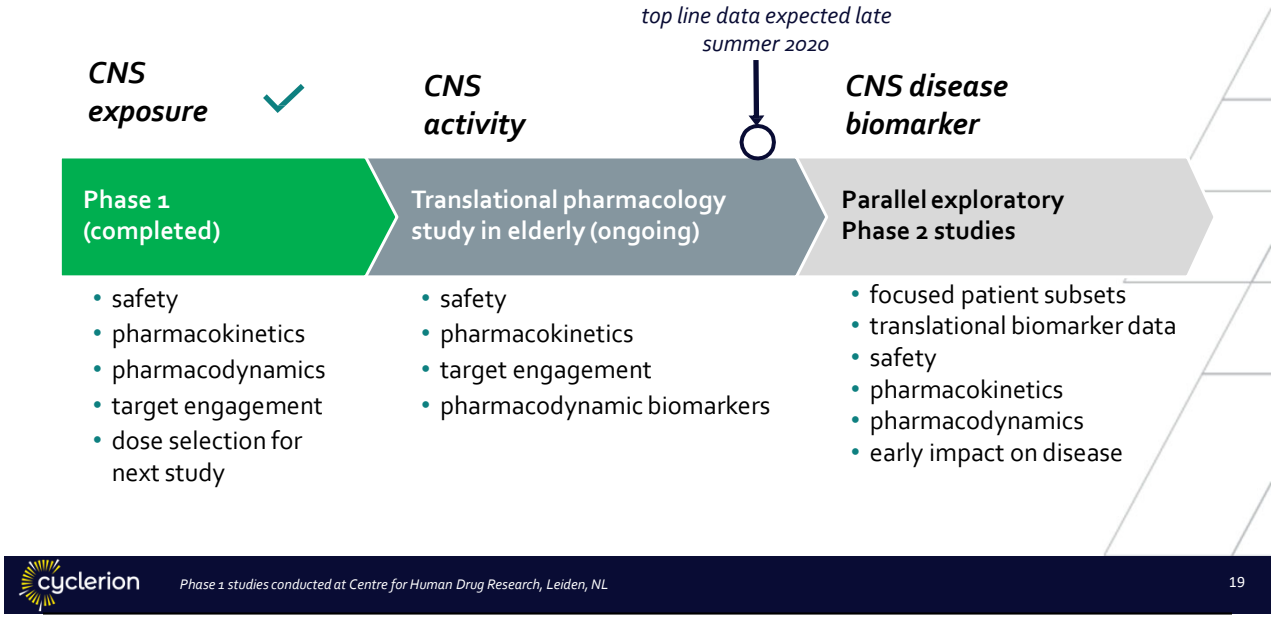
**Andy Busch (00:23:48):**

Overall, we developed a very attractive nonclinical profile, which we concluded needs to, and warrants, clinical development. We do see, as described, a pharmacological activity across distinct important domains for neurodegeneration. We do believe that the preclinical results were nicely designed to get directly translated in relevant clinical settings. We do find very significant CNS exposure and target engagement demonstrated in multiple species. We do see no evidence of CYP enzyme inhibition, and also the compound is no P-gp substrate. Finally, we have a nonclinical toxicology profile, which is consistent with other sGC stimulators in development, or which have been approved. I think all those criteria made it very clear that we have all the reasons to advance this compound to clinical development. About this clinical development, you'll hear now from Chris Winrow, our project leader for the compound IW-6463. Chris.




**Chris Winrow (00:25:20):**

Great, thank you, Andy. Certainly this is an exciting time for IW-6463. And as you can see, we're really at an important aspect of the program development. We are taking a rational approach for indication selection and we've conducted two phase one studies that I'll be going into more detail. The data from these phase one studies really has served to inform, and will serve to inform, our clinical development. We completed a phase one study, this is our first inhuman study, and had a successful study where we identified well tolerated doses and achieved our targeted CNS exposure. We have more recently conducted an elderly translational pharmacology study. This study has been focused on CNS target engagement, and will read out later this summer. We've really taken an opportunity here, as you heard from Andy, to look at which aspects of what we've observed in the nonclinical space is exciting, effects on key hallmarks of neurodegenerative disease, which of these we will be able to look at clinically and find true translation. The next slide.




**Chris Winrow (00:26:37):**

This slide lays out our early development strategy. As you can see, it is a biomarker focused strategy, and really enables us to move and gain a lot of insights from each of our studies to inform upon the next stage. In terms of our first study, the phase one first in human study, really the key goal there is to confirm safety and exposure of the molecule. We conducted this study and incorporated, in addition to plasma pharmacokinetics, a single cerebral spinal fluid set of samplings from the subjects. This enabled us to look at exposure of IW-6463 in the CNS for the first time. Again, this is a really exciting program. This is the first CNS penetrant sGC stimulator to enter development. And we want to learn as much about the molecule as we can.

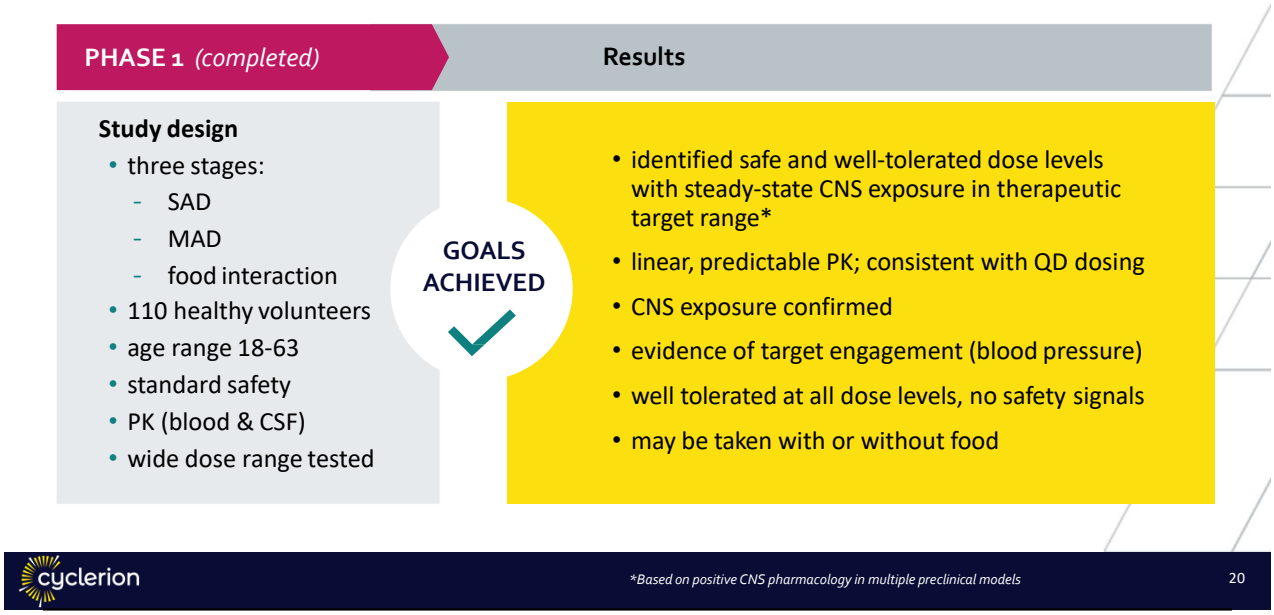
**Chris Winrow (00:27:33):**

This enabled us to look at a range of doses, which we then were able to select from and progress into our next study. That second study is a translational pharmacology study, this is conducted in elderly individuals. Just to note that, in addition to it being important to determine safety and pharmacokinetics in this elderly group, we also have an opportunity here to take multiple cerebral spinal fluid samples. And this would now for the first time, enable us to look at target engagement within the CNS. So in that space, and I'll go into this in a little more detail, we're able now to look specifically at cyclic GMP levels, and you'll recall from earlier in the presentation, this is directly produced from activating soluble guanylate cyclase. So an important aspect now to demonstrate CNS activity. Furthermore, this elderly study offered us a unique opportunity.

**Chris Winrow (00:28:31):**

During the normal aging process, nitric oxide bioavailability and nitric oxide signaling is impacted. This translates into effects on endothelial cell function and has multiple effects on different physiologies, including things like blood flow. So we have an opportunity to build in some additional measures to look at what aspects of our nonclinical hallmarks may translate into the clinic. I'll be going into that in a little more detail. We're expecting top line data from this study later this summer. So we're

in a really exciting time now and eager to understand more about these studies. We'll then be progressing further into our parallel phase two studies. And you'll be hearing more about those exciting studies in patients in the subsequent section. On the next slide.

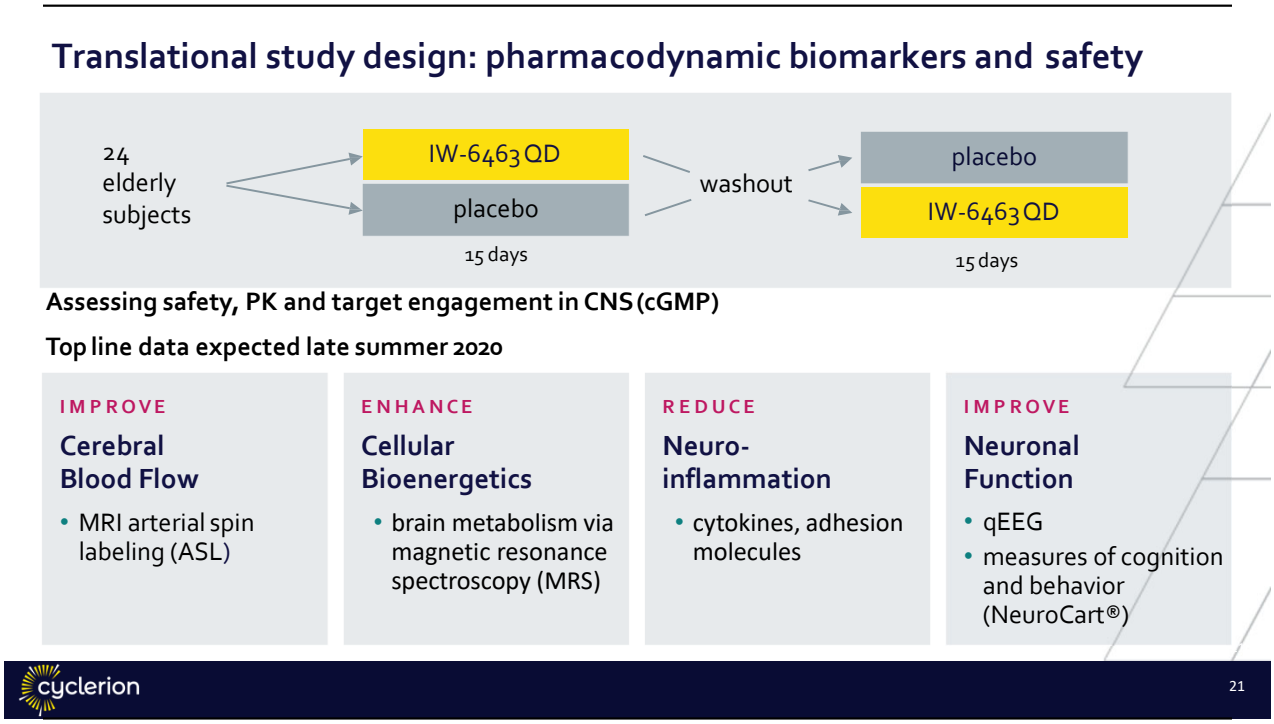



**Chris Winrow (00:29:25):**

Our phase one studies were conducted at the Center for Human Drug Research in the Netherlands. This is a premier clinical research site focused primarily on neuroscience investigations, and really we were able to conduct some innovative studies, even in the phase one space. Our first in human study combined three stages, a single ascending dose, a multiple ascending dose, and a food interaction study. This enabled us to move quickly through development and at the same time obtain a wealth of data from these studies. We examined 110 healthy volunteers. The age range was between 18 and 63. We did standard comprehensive safety assessments at the site. And in addition to looking at blood sampling, as I mentioned earlier, we conducted CSF sampling, which enabled us to look not only at exposure in the plasma, but exposure of IW-6463 within the central nervous system. And we examined a wide set of those ranges.

**Chris Winrow (00:30:26):**

This trial was successful. We identified safe and well tolerated dose levels with steady state CNS exposure. And these were within the target range that we had identified based on the pharmacology that you heard about earlier across multiple preclinical models. We observed linear predictable pharmacokinetics, and this is consistent with once daily dosing, a very important aspect of this molecule. We found clear CNS exposure, good levels of exposure within the CNS. We also observed evidence of target engagement in the form of mild decreases in blood pressure. This is something that is aligned with the sGC mechanism and is observed with other sGC stimulators. Importantly, IW-6463 was well tolerated at all dose levels. We saw no safety signals, no serious adverse events, any adverse events that were observed were mild. This enabled us to progress further into development. Also, importantly, we observed that IW-6463 could be taken without respect to food. This, of course, is important in the patient populations that we're interested in helping, both in terms of compliance and convenience for dosing. The next slide.




**Chris Winrow (00:31:42):**

We also conducted a translational pharmacology study in elderly volunteers. This was also conducted at the Center for Human Drug Research in the Netherlands. We have conducted this study with 24 elderly subjects enrolled, 24 subjects completed the first parallel phase of the study and 12 subjects completed the full crossover study. This was due to regulations that were imposed as a result of COVID in the Netherlands, but importantly, the design of our study and our analysis of the design give us confidence that our data analysis will not be impacted.

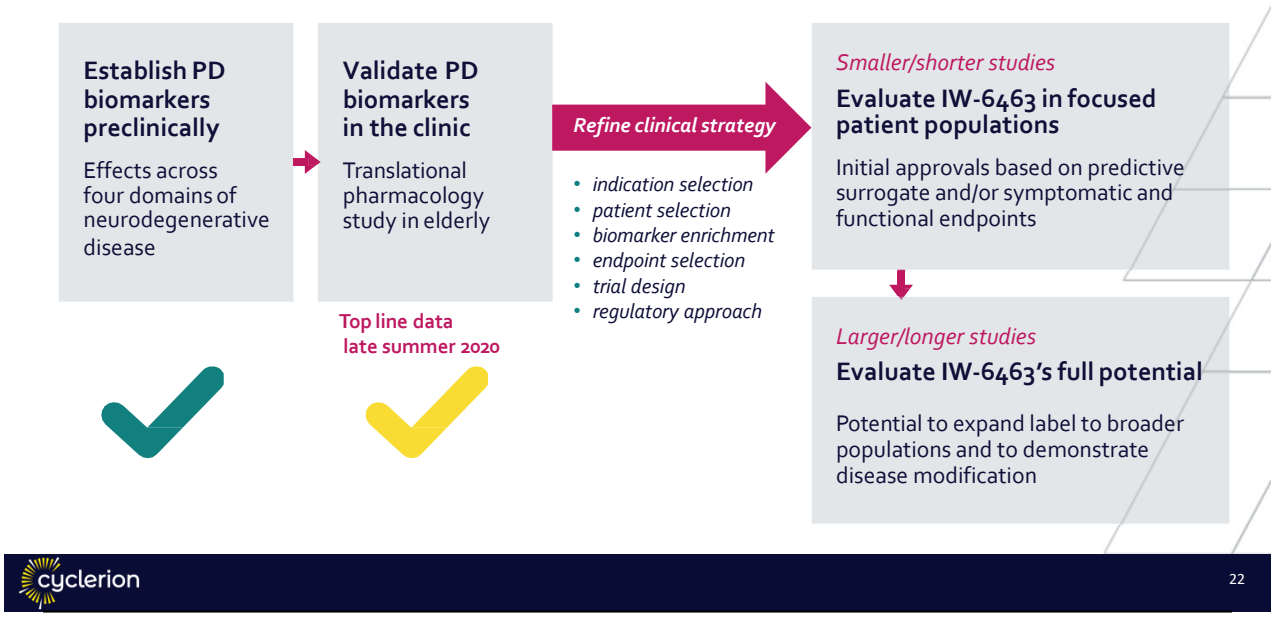
**Chris Winrow (00:32:24):**

The key attributes here, again, this is the first time we're looking at an sGC stimulator, that's CNS penetrate, are assessing safety, and it's key that we assess the safety in the elderly, and also the pharmacokinetics, both in the plasma and the CSF. As I mentioned earlier, we incorporated a number of cerebral spinal fluid sampling events within this study. This really now for the first time enables us to look directly at cyclic GMP levels within the central nervous system to confirm target engagement. The top line data is expected, as mentioned, later in the summer. I also wanted to highlight that this is a really a unique opportunity. As we age, we do see changes in nitric oxide signaling, as I mentioned earlier, and this can manifest across a range of physiologies. For our purpose, we want to understand how well the exciting observations we saw in a nonclinical space are translatable into people.

**Chris Winrow (00:33:25):**

To do that, we've incorporated a number of different measures that we'll be examining in the study. To look at improvements in cerebral blood flow, we've incorporated arterial spin labeling, examined by MRI. We'll also be looking at bioenergetics, and in that case, using the noninvasive magnetic resonance spectroscopy to look at metabolites within the brain. We'll also be examining neuro-inflammatory markers. We have CSF samples, as I mentioned, and we'll be able to look at different cytokines and other molecules that are associated with neuro-inflammation. Finally, we're looking at neuronal function. We've incorporated

quantitative electroencephalography. This is a means to measure cortical brain activity, and we'll be able to compare that to our nonclinical observations as well. CHDR has developed a battery of cognition and behavioral assessments that we've incorporated into the study in the form of the NeuroCart©. So we're really excited about this study. We have a lot of data that has the potential to read out later this summer, and we'll be excited to keep you updated as we analyze those. The next slide.

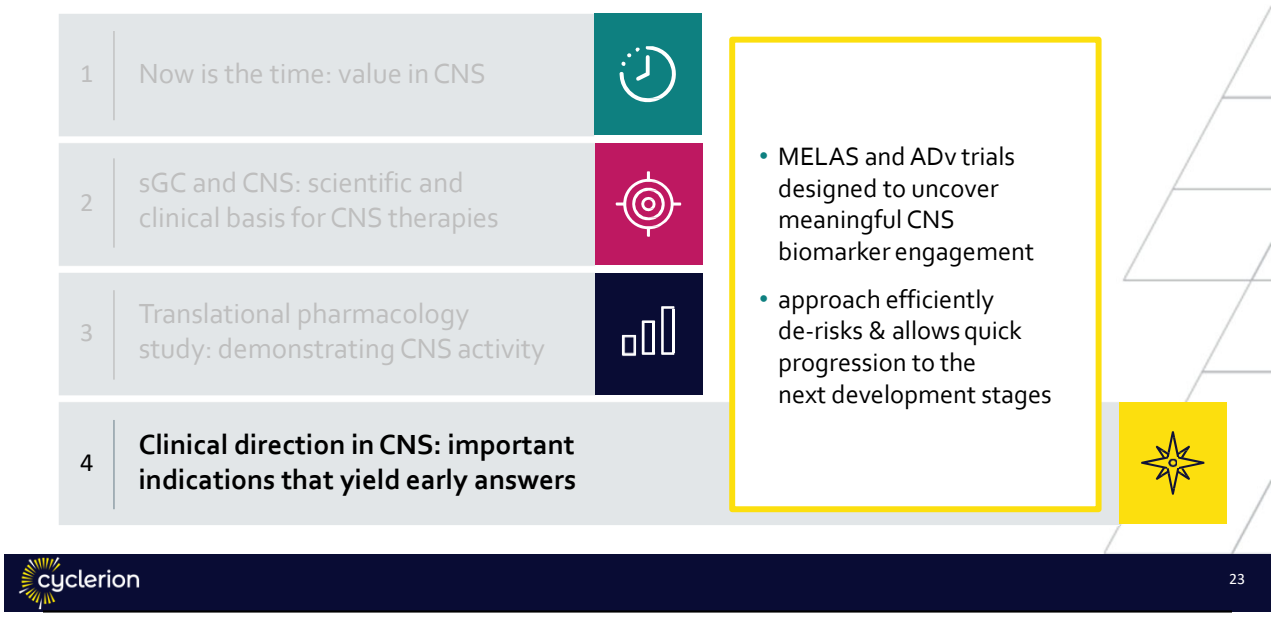



**Chris Winrow (00:34:36):**

Finally, I just wanted to use this slide to highlight the approach that we've been taking. With the first CNS penetrant sGC stimulator in development, we understand that we want to take as many opportunities to understand as much as we can about the molecule. From the nonclinical side, we've seen really exciting opportunities impacting the hallmarks of neurodegenerative diseases. Across these four hallmarks, we've really worked to validate and incorporate measures within our translational studies to see what these effects might be within the clinical population. We're expecting data later this summer, and really, we'll be taking the opportunity, not only to look at this biomarker data, but all the data to refine our clinical strategy.

**Chris Winrow (00:35:24):**

That comes in the form of opportunities for different indications, patient selection, looking at enrichment for different biomarkers, endpoint selection, how we can design our trial differently, and also helps us in having productive discussions with regulators. We have taken the opportunity to begin development of smaller, shorter studies in focused patient populations and that's the subject of the upcoming section that you'll be hearing about. At this point, I would like to thank you for your attention and turn it over to our Chief Medical Officer, Chris Wright.

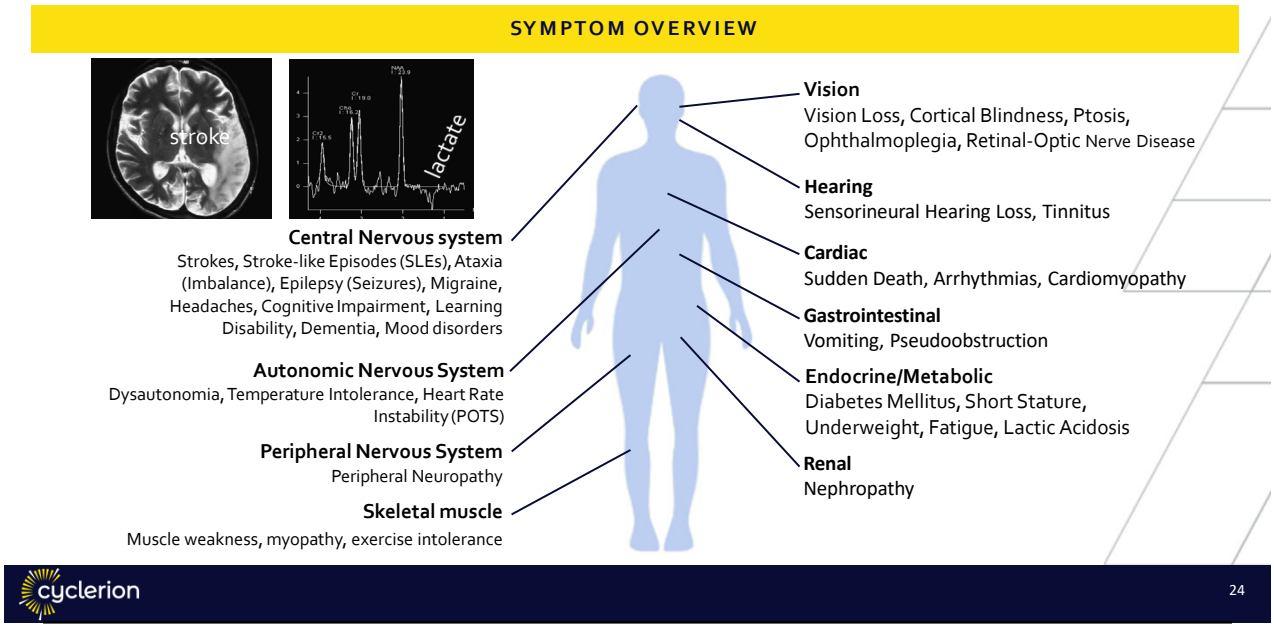



**Chris Wright (00:36:05):**

Great. Well, thank you, Chris. So in this next section, we're going to outline our development approach to our two initial clinical indications selected for 6463. These are mitochondrial disease, MELAS, and Alzheimer's disease with vascular features or vascular pathology. We have identified some strong scientific rationale for these indications, there's high unmet needs, and we've also developed some really efficient trial designs as our initial investigations into these areas. This provides us with the opportunity to understand our mechanism and whether it's having an important impact on these key features of the underlying disease pathophysiology. We believe this will mitigate the risk around development in these areas, and it provides us with direction for our later stage studies using biomarkers and clinical endpoint approaches.

**Chris Wright (00:37:03):**

The first disease area we'd like to cover is MELAS, and we're really excited to have Dr. Marni Falk here with us today to cover the clinical aspects of MELAS and the unmet need and patient selection there. Dr. Falk is a professor of human genetics at the Children's Hospital in Philadelphia and Director of the Mitochondrial Medicine Frontier Program. I think we're switching over and if you could try to unmute yourself, Dr. Falk, that would be great.




**Marni Falk (00:37:39):**

Yes. Can you hear me?

**Chris Wright (00:37:41):**

That's perfect. Thank you.

**Marni Falk (00:37:43):**

Okay, terrific. Well, I'm really excited to be here with everybody this morning. I'm sorry that I'm on audio only, but hopefully you can hear me okay. As Dr. Wright mentioned, I'm the Director of the Mitochondrial Medicine Program at Children's Hospital, Philadelphia and University of Pennsylvania. And we take care of people with inherited disorders of mitochondrial function. One of the most severe is mitochondrial encephalopathy with lactic acidosis and stroke-like episodes. It was one of the first mitochondrial diseases ever discovered more than three decades ago, and it goes by the acronym of MELAS. It's genetically defined, mainly caused by mutations in the DNA within the mitochondria that impair the ability of the mitochondria to make energy. Unfortunately, it causes very serious brain problems, central nervous system, but also multisystemic diseases. There are no approved therapies, although we're starting to gain insight into the pathophysiology, which again is why we'll share with you, we're really excited to see what IW-6463 can do.

**Marni Falk (00:38:50):**

As you can see in this schematic of a person, there's really no organ that couldn't be affected. And while lots of people it turns out carries this mutation, not everybody gets all of these symptoms. It's very heterogeneous and there's both different genetic mutations that cause it and symptoms that can occur. But the most devastating, that cause death and severe dysfunction, are the neurologic features. And it can involve the central nervous system, the autonomic nervous system, and the peripheral nervous system. One of the biggest problems, and probably why it got diagnosed as one of the first syndromes ever is that it causes strokes. As you can see on the upper left image, it causes strokes in high energy demand areas. These aren't blood clot strokes that follow a

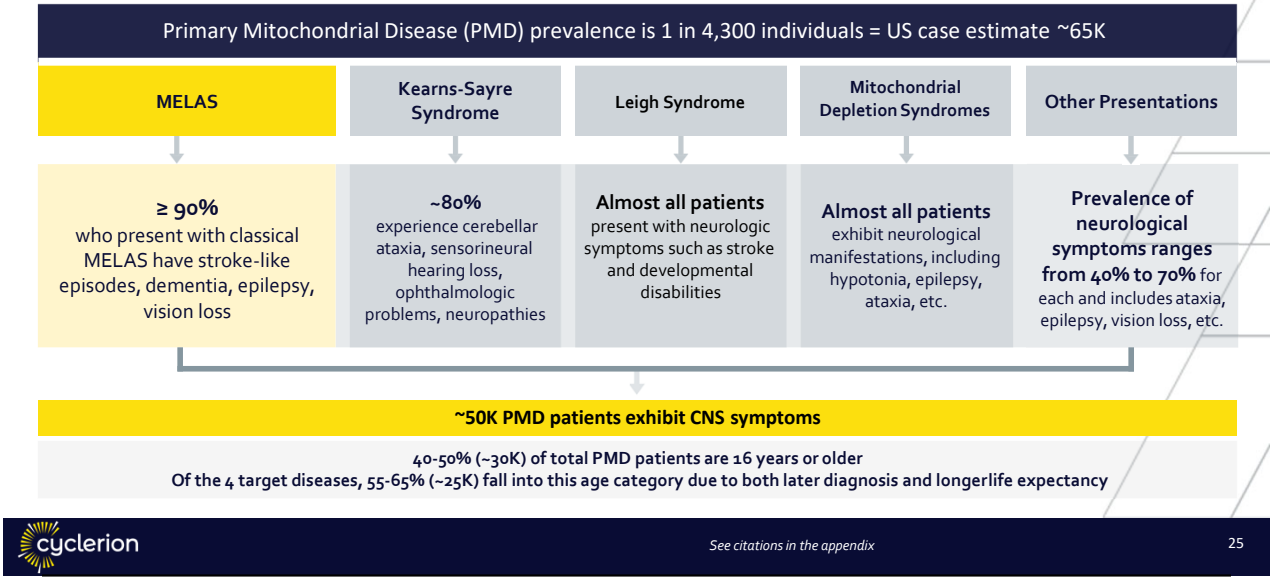
vascular distribution or embolic strokes. These are metabolic strokes. These are high energy demand areas that are really quite sick. We know that it has to do a little bit with the vascular endothelial reactivity, and also just a mismatch of blood flow to demand. Often these happen under stress.

**Marni Falk (00:39:53):**

What you can see in the right, is what was mentioned before, an example really of metabolism in the living brain, it's called magnetic resonance spectroscopy. And if you put your voxel or probe over the area of the brain of interest, you can start to see the chemicals in that region, and where it says lactate, there shouldn't be anything there, nothing really detectable. So there's too much lactic acid because the cell can't make, or the brain can't make energy or ATP properly through the mitochondria. So it has to do it anaerobically and that leads to lactic acid buildup. These are really very troubling disorders. There are no approved therapies. We've started to learn over the last decade around the world that we can give some medications that improve nitric oxide flux, simple things like Arginine or citrulline. These can help both to prevent the strokes and also stop the strokes when they're happening. So it's super promising, but we don't know that we have the most potent therapies yet to target this pathophysiology. Next slide.

## Focused MELAS trial population for trials; potential for broader use

*US prevalence of mitochondrial disease and CNS symptoms*




**Marni Falk (00:41:05):**

Now you understand that mitochondria diseases are pretty heterogeneous. They're a rare disease, but collectively they're the most common inborn error of metabolism affecting at least one in every 4,300 people, which in the US translate to a rough estimate of about 65,000 people. There's lots of different presentations. We discussed MELAS. There's just some other very common presentations, Kearns-Sayre syndrome, Leigh syndrome, which is primarily pediatric, depletion syndromes, where you don't have enough mitochondria, and really just the severe range of multisystem disease. But us and others have looked into what percentage of the time you get neurologic manifestations. And unfortunately, it's really high. Once you manifest with these syndromes, one of the most devastating problems is neurologic disease. We estimate while MELAS is a very confined set of very cleanly delineated genetic causes that present with these strokes as well as dementia and seizures and blindness and hearing loss and other problems, all told, all mitochondrial disease patients are at very high risk for neurologic problems. Really under stress is when they come out the most and they're most at risk for stroke.

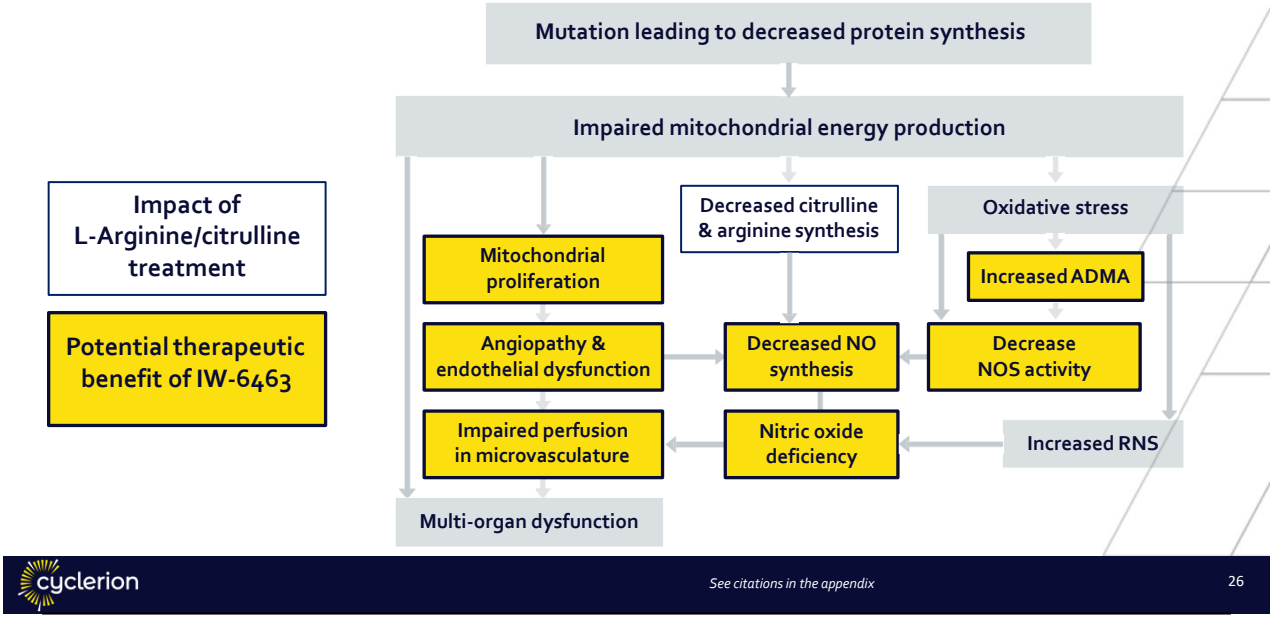
**Marni Falk (00:42:18):**

One of the things that we do know is that a lot of the time, not always, but in many, especially with the neurologic problems, there's a nice biomarker of mitochondrial disease that we can follow, and that is lactic acid. While it's not perfect for every type of mitochondrial disease, it is quite good in people with the neurologic manifestations. We're really excited about this study, that's going to really target what patients prioritize as their most important problems that they'd like to have treated, which are the neurologic problems, and for which we really don't have a great therapy.

**Marni Falk (00:42:53):**

We're also excited about the design of this trial, because it's going to focus in what the FDA advises should be really targeted genetically similar subset of patients with clinical symptomatology. And if you can

show there in a small disease population, a therapeutic benefit, later you could extend that to the more heterogeneous causes that might be overly complex to solve in one full basket study. We believe that this is really an exciting opportunity to bring a therapy that's targeting known pathophysiology in a more potent way in patients who can really benefit directly, potentially from the approach. The next slide.




**Marni Falk (00:43:39):**

IW-6463 will potentially impact the pathophysiology of MELAS at multiple points. As I mentioned before, the mutations in the mitochondrial DNA, often in tRNA, our genes involved in mitochondrial translation, have a common effect. They don't make energy properly, or ATP, as the end result. And we know now that there's reductions in critical amino acids involved in nitric oxide production. That's why some of the therapies that we use, because we have nothing else available, are tried. We do use Arginine off-label to treat the strokes, and you can see that would work by repleting the citrulline arginine that becomes deficient. But IW-6463 can also directly impact this pathophysiology at several points. So we hope that it'll be even more potent and safe. I'm excited to pass along Chris to you, who will explain specific clinical trial plans that we hope will get underway very soon to test the efficacy of this drug and this disease.

**Chris Wright (00:44:55):**

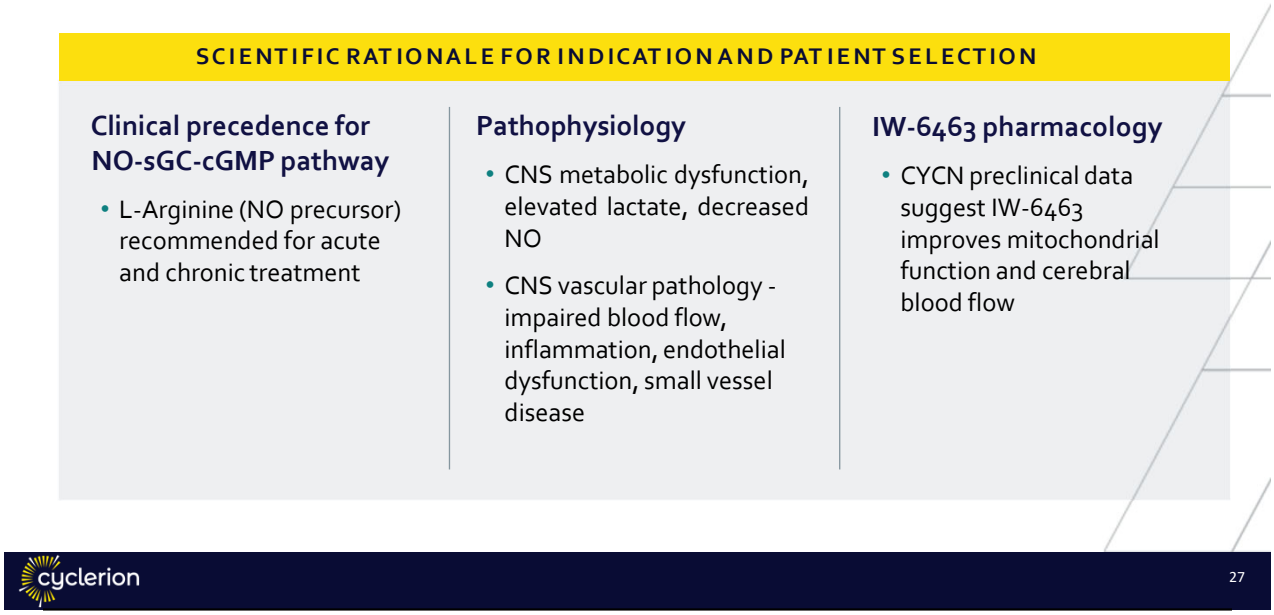
Great. Thank you very much, Marni. Could you go back to the prior slide please? Great. I just wanted to take you through on a little bit more detail about what we think the therapeutic potential of 6463 is on the impacts of mitochondrial disease on mitochondrial energy production. As Marni mentioned, in the context of the energy defect, we have decreasing levels of citrulline and arginine, and those can be supplemented. But in addition, MELAS leads to a number of other pathophysiologic elements. So there's a further decrease in NO synthesis and worsening NO deficiency because of vascular dysfunction. There is also a compensatory mitochondrial proliferation, which also impacts the vasculature, and both these factors which impact the vasculature can cause decreased blood flow and additional oxidative stress.

**Chris Wright (00:46:00):**

As you may know, oxidative stress leads to decreased production of NO, which leads to further NO depletion. Well, citrulline and Arginine can help ameliorate part of the disease defect, as you can see here, based on what we've learned about 6463, we really feel that it could have a broad

impact across multiple aspects of the pathophysiology, as you can see, outlined here in the yellow boxes. So we're really excited about the breadth of this mechanism in this population. And we're excited that we may have some meaningful relief for patients that are suffering from not only the CNS symptoms, but also potentially the systemic symptoms. Next slide, please.

## MELAS: strong supportive data for NO-sGC-cGMP pathway involvement

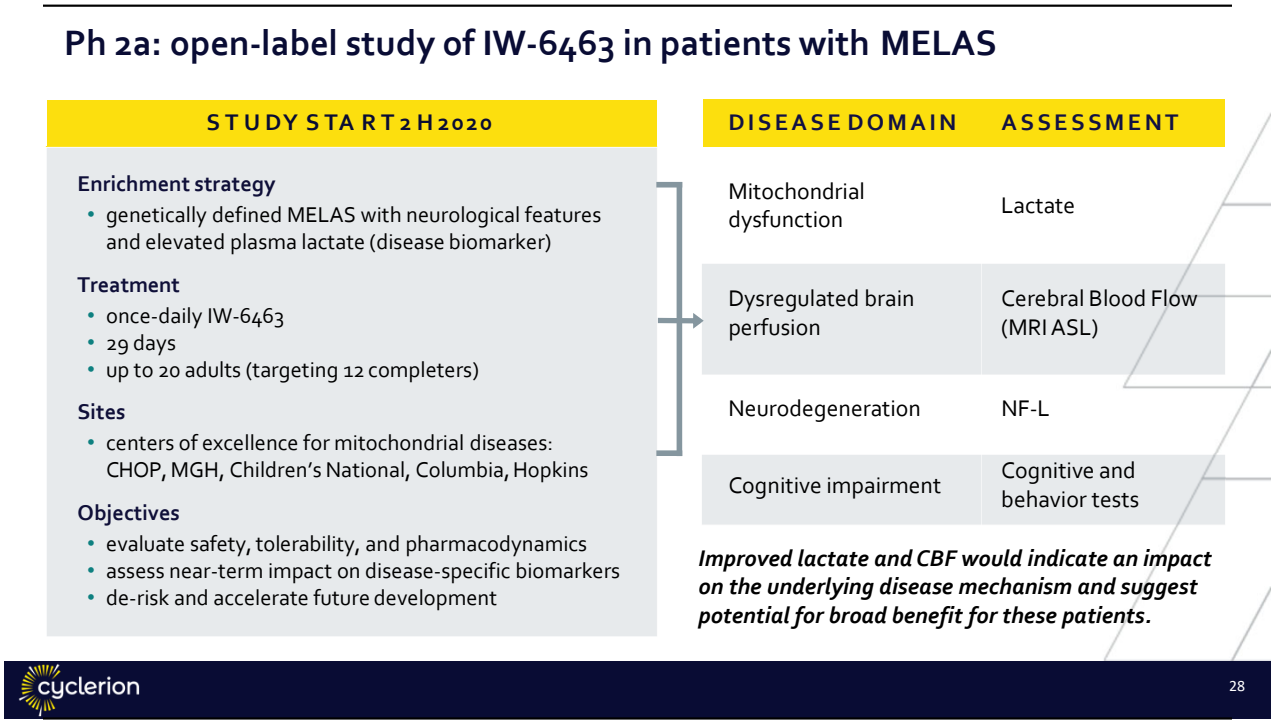



**Chris Wright (00:46:44):**

There's a really strong, supportive, scientific rationale for using a centrally penetrant sGC stimulator to target MELAS and other mitochondrial disorders with CNS features. For this clinical precedence, as we discussed for NO precursors, such as Arginine, which are used in practice acutely as well as chronically, primarily targeting the stroke symptoms. However, the effect of NO donors or the precursors is expected to be narrower than 6463 as I described earlier, and the utility beyond stroke for other symptoms may be limited. So from the pathophysiology of MELAS, what we really like in terms of the match is that it features the CNS metabolic dysfunction, as well as the CNS vascular pathology. And really, both of these areas are areas that we know this sGC mechanism can have an impact.

**Chris Wright (00:47:44):**

In addition, we have a very detailed preclinical pharmacology support from 6463, some of which Andy outlined for you earlier. But we've seen that 6463 can increase and normalize ATP production in human mitochondrial disease cell lines. We also have data showing that it increases the expression of genes that are beneficial to mitochondrial function. And of course, as he showed you, it increases blood flow to the CNS and vascular health as well. Next slide please.




**Chris Wright (00:48:25):**

On the basis of all this information, we designed an open label study to evaluate once daily 6463 for up to 29 days and up to 20 patients with MELAS using an objective CNS biomarker approach in a well-defined population. We expect this study to start later in Q3. As Marni mentioned earlier, it's really important that we identify a homogeneous population as heterogeneity in mitochondrial diseases is known to be a challenge in this area, and it's the reason that many programs did not meet their goal. So with advice from experts, such as Dr. Falk and others, we've carefully selected a genetically and phenotypically defined MELAS population with CNS symptoms, and that is also required to have elevated lactate levels, which is one of our key biomarker end points.

**Chris Wright (00:49:24):**

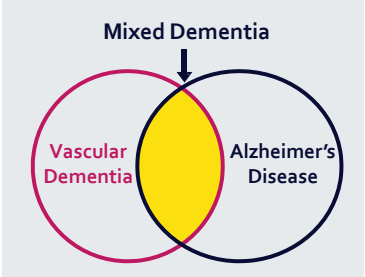
As was mentioned, lactates elevated, it's a required aspect of the MELAS diagnosis as part of the abbreviation of lactic acidosis and so it's directly related to mitochondrial dysfunction and also it's correlated with symptom severity and disease progression. So there's both a mechanistic and a clinical connection to that as a biomarker, making it quite attractive. We're working with several centers of excellence such as Children's Hospital of Philadelphia, MGH, Columbia Children's National, Johns Hopkins, and our planned study evaluates safety, tolerability, and utilizes the biomarker approach to understand the impact that 6463 could have in these patients in need. So changes in lactate levels from baseline, sort of treatment effects, would be a key assessment. They're closely related to the underlying pathophysiology of the disease. So if we were to see changes there, that would give us very strong evidence that we're having impact on the underlying cause of the disease.

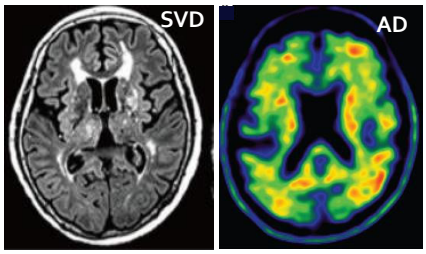
**Chris Wright (00:50:32):**

We'll also look at cerebral blood flow as this is dysregulated in MELAS, and it's one of the key disease domains where we'd expect 6463 as an sGC stimulator to have an impact. And then further, we'll assess neurofilament light chain and perform some cognitive and behavioral tests. It's a relatively short study to see changes in these measures, but

it'll provide us with some experience in this population. And if we did see some changes in neurofilament light chain or cognitive functioning, that would be very, very promising and exciting too. And if we saw this improved lactate, as I mentioned, with increased cerebral blood flow, that would indicate that we're having an important impact on the underlying mechanism of the disease and also could support us moving forward rapidly with a biomarker registration approach given this as an orphan population with no approved treatments. Next slide, please.

## Vascular pathology in dementia – clinical perspective




**PATIENT PRESENTATION & CHARACTERISTICS**

- AD & vascular dementia - two most common dementias
- pure forms exist, but vascular pathology widely prevalent in AD
- mixed dementia = broad area of overlap
- subcortical small vessel disease (SVD) in a significant portion
- mixed dementia patients more rapidly progressive disease, higher symptom severity

**UNMETNEED**

- ~2M US patients; incidence increasing with aging
- symptomatic treatment for AD – modest, brief benefit
- no disease-modifying therapies, none targeting the vasculature

| Dementia type | Pathophysiology |
|---|---|
| Alzheimer's | • neurofibrillary tangles<br>• amyloid plaques |
| Vascular | • impaired brain blood flow |
| Mixed Dementia | • combination of the above |

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**Chris Wright (00:51:40):**

For the next section, I'd like to move on to discussing Alzheimer's disease with vascular pathology. Again, we're quite fortunate to have Dr. Eric Smith joining us today. Dr. Smith is a neurologist with a focus on the vascular contributions to dementia. He's a professor of neurology at the University of Calgary, and he's also the Katthy Taylor Chair in vascular dementia. So I'd like to pass the floor on to Eric. And if you could please unmute, that would be great.

**Dr. Eric Smith (00:52:13):**

Thank you, Chris. Yeah, it's Eric here. Can you guys hear me okay?

**Chris Wright (00:52:17):**

Yep.

**Dr. Eric Smith (00:52:19):**

Very good. Okay, thanks. I'm also on the phone, so you won't have a video of me inflicted on you, which is okay. I've got more of a radio voice than a TV face, I think. So it's a pleasure to be here today. Thanks so much. I'm going to talk to you about vascular contributions to neurodegeneration and dementia. I'm a clinician scientist, so I'm a practicing clinician. I run a dementia clinic and I'm a member of the Calgary Stroke Program. My interests are in how the vascular disease contributes to age related decline and risk for dementia. The two main neuro pathologies of dementia are Alzheimer's disease neuro pathology, and vascular neuro pathology. Statistical modeling studies suggest that vascular disease accounts for about a third of all cases of dementia, and Alzheimer's disease about half. So together the two of them are the majority of causes of dementia, and these have to be the targets for public health promotion, prevention, and treatment, clearly.

**Dr. Eric Smith (00:53:16):**

However, these two disease processes are very closely linked. In the brains of many persons with dementia, you'll see evidence of both processes as shown in the Venn diagram in the top left. Out of all patients with dementia, about 80% have one or more small infarcts in the brain or white matter changes consisting of demyelination,

oligodendrocyte loss accompanied by micro infarcts and arteriosclerosis, this is evident on clinical neuro imaging, such as the MRI scan at the bottom left, as areas of white matter hyper intensity. Which areas of increased water content in the white matter of the brain did a loss of these tissue elements in the slide labeled, or the panel labeled SVD, which stands for small vessel disease. These changes are evident on clinical neuroimaging. They're part of the workup and diagnosis for patients with dementia.

**Dr. Eric Smith (00:54:12):**

About 30% of all patients with Alzheimer's disease will have evidence of these changes, like extensive white matter changes or multiple infarcts such that it would be clinically diagnosed with what's called a mixed dementia, meaning a combination of both vascular disease and Alzheimer's disease. Sometimes the vascular contribution is evident because there's been a clinical stroke followed by a decline, but the more common scenario is that the vascular contribution is not recognized until neuroimaging reveals these changes in the brain. We can recognize Alzheimer's disease by other markers such as the amyloid PET scan, which is shown in the panel to the right of the MRI scan and labeled AD for Alzheimer's disease. As I said, these diseases so often co-occur that people hypothesize they may be more intimately connected than previously thought. For example, both of these diseases are marked by dropping blood flow, or perfusion of the brain. The reason for this is intuitive in patients with vascular disease, but it's also seen in Alzheimer's disease.

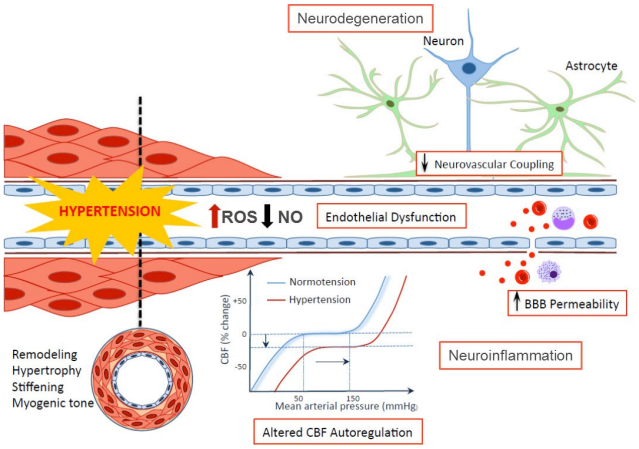
**Dr. Eric Smith (00:55:21):**

The traditional thinking has been that this drop in perfusion is related to atrophy of tissue. There's just no longer as much tissue that's needing blood flow. But modeling studies from the Alzheimer's Disease Neuroimaging Initiative, for example, show that this drop in perfusion is a very early phenomenon in Alzheimer's disease, suggesting it may be causative in some way or accelerating Alzheimer's disease neuropathology rather than merely being a consequence. It's also the case that sporadic Alzheimer's disease appears to result from a failure to clear a-beta peptides from the brain. These peptides are cleared along perivascular pathways. So dysfunction of the vasculature may also contribute to Alzheimer's disease formation by preventing clearance of a-beta from the brain and it aggregates as senile plaques, the plaques we think lead to the neurofibrillary tangles, and then the neuro degeneration that occurs in Alzheimer's.

**Dr. Eric Smith (00:56:23):**

I think as people probably know, there's been a large pharmaceutical development program targeting the plaques in Alzheimer's disease so far with mixed results, with failures of multiple monoclonal antibodies and mixed results for the aducanumab antibody. What has been missing so far from the armamentarium for disease modifying therapies against Alzheimer's disease are drugs that are targeting specifically the vasculature. So go to the next slide, please.

## Vascular pathology: a key contributor to dementia




**SUPPORTIVE EVIDENCE**

- risk factors and common comorbidities: DM, HTN, HL, Smoking, CAD
- ApoE risk partly mediated by endothelial dysfunction and BBB breakdown
- brain ischemic changes present in dementia, including AD; possibly independent disease progression risk factor
- vasculature implicated in a-beta brain clearance, a process that fails in AD

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**Dr. Eric Smith (00:57:02):**

There's a number of reasons why targeting the vasculature, I think, may be a promising way to approach Alzheimer's disease with the vascular component. The main cause of the vascular disease in the brain of persons with dementia is what's called small vessel disease, meaning diseases of the small arterials and small arteries. Hypertension is a major risk factor, both for stroke, but also for vascular and mixed dementia. In this condition, you get remodeling of the vessel wall, hypertrophy and thickening. You get stiffening which may alter blood flow to the brain and may decrease clearance of a-beta peptides. There is also endothelial dysfunction, which results in alterations in permeability of the blood brain barrier or BBB. That is hypothesized to lead to leakage of toxic molecules from the inside of the lumen, into the brain parenchyma, these processes then secondarily lead to neuro-inflammation, which has been closely linked with the neuropathology and decline in dementia.

**Dr. Eric Smith (00:58:09):**

Other lines of supportive evidence include that the epidemiology of dementia is largely a vascular epidemiology. Risk factors include diabetes, hypertension, and smoking, all identified as among the top eight potentially modifiable risk factors for dementia by the Lancet Commission Report. Hyperlipidemia, coronary artery disease, high BMI in midlife, also related to dementia risk, and not just dementia in general, but also Alzheimer's disease risk specifically. APOE is a known risk factor for Alzheimer's disease, but it's also a risk factor for vascular disease. It's been linked with endothelial dysfunction and blood brain barrier breakdown. Brain ischemic changes are present in dementia, including Alzheimer's disease as discussed. Drop in blood flow is an early change in Alzheimer's disease and it may be a contributor to disease progression.

**Dr. Eric Smith (00:59:07):**

We know that for patients with a given level of Alzheimer's disease, those with more brain MRI changes due to vascular disease have a more aggressive course and worse performance. Finally, as discussed, the vasculature has been implicated in the normal process of flushing toxic

molecules, like a-beta peptides out of the brain, and that the process has failed in AD, and maybe related to vascular dysfunction and remodeling. For all of these reasons, sGC stimulators appear to have a promising role to potentially modify the course of vascular and mixed dementia with Alzheimer's disease. So I'll now turn it back over to Dr. Wright to explain some of the plans for clinical trial in this patient population.

## AD with vascular pathology (ADv) – focused mixed dementia subset

Defined population well suited for treatment with IW-6463

**DISEASE RATIONALE FOR PATIENT SELECTION**

**Pathophysiology**

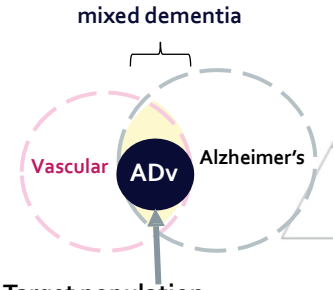
NO dysregulation, endothelial cell loss, impaired blood flow, vascular leakage, inflammation, neuronal dysfunction, and neuronal loss are major contributing factors to rapid disease progression

**Standard of care**

No approved therapies to treat vascular dementia.
AD therapies offer limited benefits; not disease modifying

**Pharmacology**

Our preclinical data suggest IW-6463 has potential to improve cerebral blood flow, endothelial health, neuroinflammation, and cellular energetics as well as prevent neurodegeneration




**Target population**

ADv: an identifiable subset of mixed dementia patients with:

- AD pathology **AND**
- sub-cortical vascular disease **AND**
- CV risk factors

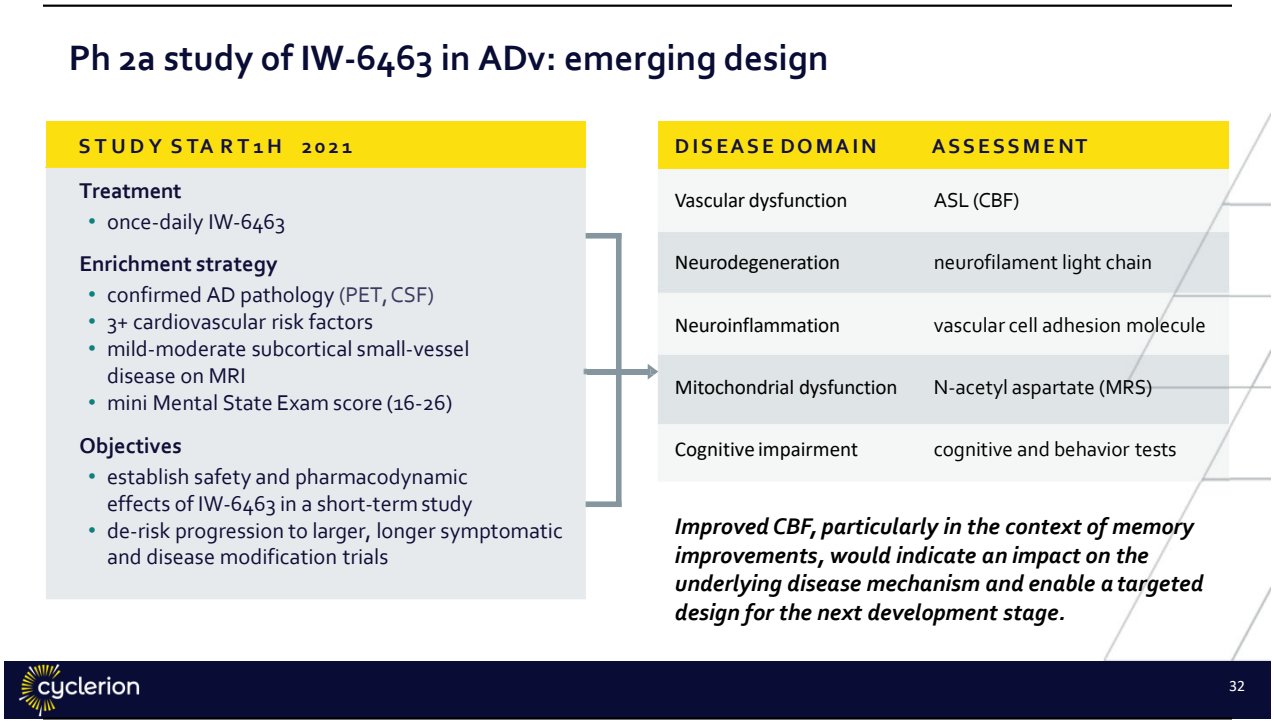
cyclerion *Alzheimer's Association,, Rizzi et al., NCI Analysis* 31

**Chris Wright (01:00:02):**

Great. Thanks very much, Eric. As you just heard from Dr. Smith, this is an area where there's really extremely high unmet need. There's millions of patients and no treatments that target this important underlying vascular pathophysiology. We believe the time is now for new approaches to these diseases. As you heard, and know therapies focusing on beta amyloid or tau so far, which are the classic hallmarks of Alzheimer's disease, so far have not really demonstrated meaningful benefits to patients in several late stage studies. So given what's known about the role of NO and the related vascular inflammatory and neuronal dysfunction in this disease, a centrally active sGC stimulator like 6463 fits well as a potential treatment for Alzheimer's disease with vascular pathology or ADv for short. This pharmacologic approach would not only increase blood flow to the brain and reverse vascular pathology, but also have benefits for neuro-inflammation, bioenergetics, neurodegeneration, and cognition.

**Chris Wright (01:01:17):**

For this initial study, we're focusing on a very targeted patient population that we believe is well suited for treatment with 6463. So 6463 may have benefits on a larger population of mixed dementia or on vascular dementia or Alzheimer's disease alone. But we're focusing on this select targeted group to optimize their likelihood of seeing a treatment response. The patients for this trial must have AD pathology. They must have the subcortical small vessel disease, as you saw on the MRI scan in the first slide in this section, and they have to have cardiovascular risk factors. Based on our discussions with experts, such as Dr. Smith and also with the FDA, this is considered a definable population that can be objectively characterized clinically for a clinical trial. The next slide, please.




**Chris Wright (01:02:20):**

In terms of our clinical trial study design, we're planning a phase two study in this population, which we expect to start in the first half of 2021. The readouts from the translational pharmacology study that Chris Winrow discussed earlier in the elderly will enable us to finalize the design of this study later this year. It's expected that this would be a randomized controlled trial with patients receiving once daily doses of 6463 or placebo. The population would be based on our enrichment strategy, as I mentioned, would include those with confirmed AD pathology. So they must have the beta amyloid PET scan or CSF a-beta tau ratios that are confirmatory for Alzheimer's disease. They must have three cardiovascular risk factors or more, and have mild to moderate small vessel disease subcortically based on their MRI scans. We would be using a well accepted scale for quantitating that.

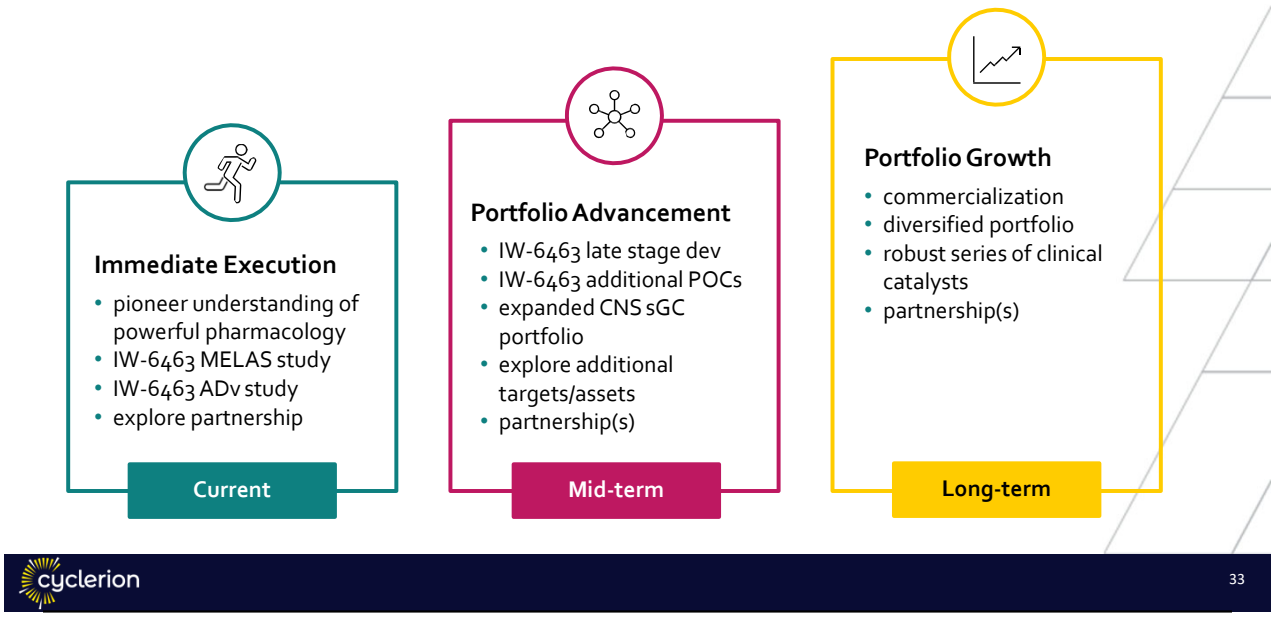
**Chris Wright (01:03:27):**

Then finally, they'd have to have a mini mental state exam score in the 16 to 26 range, which is in the mild to moderate range for cognitive impairment. We wanted the patients not to be too cognitively impaired, where you might not be able to see any improvements, or to be too mild where you would have a similar issue because they were performing so well. So given our preclinical work and the known benefits of this mechanism on cerebral blood flow and also on vascular health, our objectives in addition to safety, focus on several specific disease domains. So we'll assess the improvement of cerebral blood flow using ASL, that's arterial spin labeling, which there's noninvasive MRI technique that can help us to assess vascular dysfunction. We'll also evaluate neurodegeneration with the neurofilament light chain.

**Chris Wright (01:04:24):**

In addition, we'll assess a number of other important areas that are becoming increasingly relevant as part of understanding the pathophysiology of neurodegenerative diseases. Thinking about neuro-inflammation, bioenergetic or mitochondrial dysfunction, those are areas that are thought now more and more to contribute to the disease, and

we have the potential to impact these as well. We'll be doing a number of assessments to evaluate those. Then finally, we'll be looking at cognitive impairment using cognitive and behavioral testing. So if we were to observe improvements in cerebral blood flow, particularly in the context of memory improvements, that would be an exciting indication of impact on the underlying disease mechanism. It would provide a method for rapidly de-risking this mechanism in this indication, and also enable a targeted design for our next stages of development. So with that, thank you very much for your attention and for our outside speakers for their excellent contributions. I'd like to pass the floor on to Cheryl and Peter to wrap up the webinar.




**Cheryl Gault (01:05:41):**

Great. Thank you, Chris. And thanks again to Dr. Falk and Dr. Smith for their insights into today's discussion. As I mentioned at the start of the call, we're very excited about the potential for sGC in the CNS, and we are committed to building CNS as a core franchise going forward. In the current period, we're focused on executing our development plans for IW-6463 and the initial opportunities in MELAS and ADv are very exciting. These are two indications where the underlying biology and availability of good biomarkers, along with the valuable collaboration with expert thought leaders, gives us an increased probability of success.

**Cheryl Gault (01:06:19):**

We're also exploring a strategic R&D partnership that will allow us to fully invest in the breadth of the opportunity, which is vast. With success in the clinic, we expect to advance IW-6463 forward into late stage development and initiate additional proof of concept studies in additional indications. We also intend to build on this initial success and expand the portfolio, both in sGC and in new targets. From there, we will be well on our way to building this core CNS franchise and to helping patients suffering from serious CNS diseases. With that, I'll turn it back to Peter Hecht.

**Peter Hecht (01:06:59):**

Great, thanks everybody. This has been a very interesting and educational morning. I want to take just a minute to reiterate three key themes that we'd like you to take away from this morning's presentation. And then if there's time, we'll open up for a few questions. I hope what you've heard from us today is that this is really a great time for us to be investing our resources in the CNS area and particularly in 6463 and the NO sGC neurotransmitter system. It's clear that the CNS is coming of age. The science is rapidly evolving. We understand more about the biology, the patient, and CNS biology in general, I think, than ever before. That's allowing us to select appropriate focused patient groups to investigate our drug with and to select appropriate biomarkers that can help us in the development process. I think both of those features allow us to have a better probability of success and a faster path through development than historically has been true in the central nervous system. And you can see that in a number of companies in general industry interests these days as well.

**Peter Hecht (01:08:22):**

Second, there's a team of people here that are very experienced drug hunters. Many of them have years and years of efforts successfully in key leadership or discovery roles in this mechanism and many others in the CNS and outside the CNS, successfully bringing drugs to market and to patients. We're super excited, I think you can tell, about applying that experience and the foundational success that we've seen in this mechanism in the periphery in cardiovascular diseases, now to the CNS.

**Peter Hecht (01:09:01):**

Third, I want to emphasize something that Cheryl raised at the outset, which is that although all of our discussion today has been focused on the CNS program, again, I think you can hear our energy and enthusiasm for it, we want to reiterate that we're deeply committed to the sickle cell therapeutic area and to patients with sickle cell. We're very hard at work in wrapping up and bringing in that study and we're excited to see the data and share it with you as soon as we have it. We expect that at the

very end of the third quarter. Because of the pharmacology of olinciguat, our drug for sickle cell, and the impacts that we believe it will have in upstream and downstream pharmacology, we think there's really an important potential that that drug will deliver a really meaningful benefit for sickle cell patients and find a good place to become part of the growing armamentarium of sickle cell therapies.

**Peter Hecht (01:10:01):**

We're looking forward not only to getting that data, but to having a similar investor event with you around those data later in the quarter. Okay. So we have a few minutes, as we move to the Q&A session, let me reiterate the gratitude, particularly to Dr. Falk and Dr. Smith, for graciously sharing their time with us and with sharing their expertise around the patient and the specialties that they're both experts in. And gratitude to the team and to all of you for being with us this morning. We've gotten a bunch of questions since we announced the webinar, both from investors and from analysts. In our course of speaking with investors, we've gotten a range of questions.

**Peter Hecht (01:10:51):**

Time's very short, so I'm just going to ask two. One is to Chris Winrow, who you guys have met. I think this is a question that a lot of folks have. Chris, I think the question would be along the lines of: this translational pharmacology study that you're reporting data on soon, what's a win look like? What should we expect and how will it affect your course of advancing the drug?

**Chris Winrow (01:11:21):**

Sure. Thanks, Peter. I think success in the translational pharmacology study really will result and confirm the safety profile in the elderly population. Confirming IW-6463 exposure in the CNS, and increases in cyclic GMP in the CSF as well to confirm target engagement. We'd also look for changes in at least one biomarker. For example, that could be ASL to look at cerebral blood flow. We look at this study as informing our clinical strategy. As an example, the translational pharmacology study will really be guiding for our upcoming Alzheimer's disease with vascular pathology study that you heard about. We'll get an initial look at safety in the elderly, effects on target engagement in the forms of cyclic GMP in the CSF, and the effects of CNS activity in biomarkers. That could, for example, be cerebral blood flow, which are all relevant to Alzheimer's disease with vascular pathology.

**Peter Hecht (01:12:20):**

Great, thanks. I think we really have time for one more question. This question, I'm not sure how we'll do it, the technical challenge. If we can get through to Dr. Smith, let's see if he can answer the question, if not, maybe Chris Wright, you could take it. But I think there was a question about, in general, why we think there's potential to treat this subset of Alzheimer's with an sGC stimulator and a little bit more color on the patient population and how broad it is really, and how focused it is really.

**Dr. Eric Smith (01:12:59):**

Yeah. This is Eric Smith. I can start, and then maybe Chris could add any comments that he wants. So this patient population is well definable. They can be defined based on MRI vascular changes. MRI is routine

imaging that's done in part of clinical guidelines for care for patients with dementia. We have radiological standards and scientific standards for recognizing these types of changes and those standards reporting vascular changes on neuroimaging, which I co-funded along with Joanna Wardlaw and Martin Dichgans, published in the Lancet Neurology, cited more than 1500 times. So this has been the standard for making the radiological diagnosis. Recognizing vascular dementia as part of international classification of disease codes, which is how physicians like myself submit their billing so we're literally paid in part based on recognizing this disease entity.

**Dr. Eric Smith (01:14:00):**

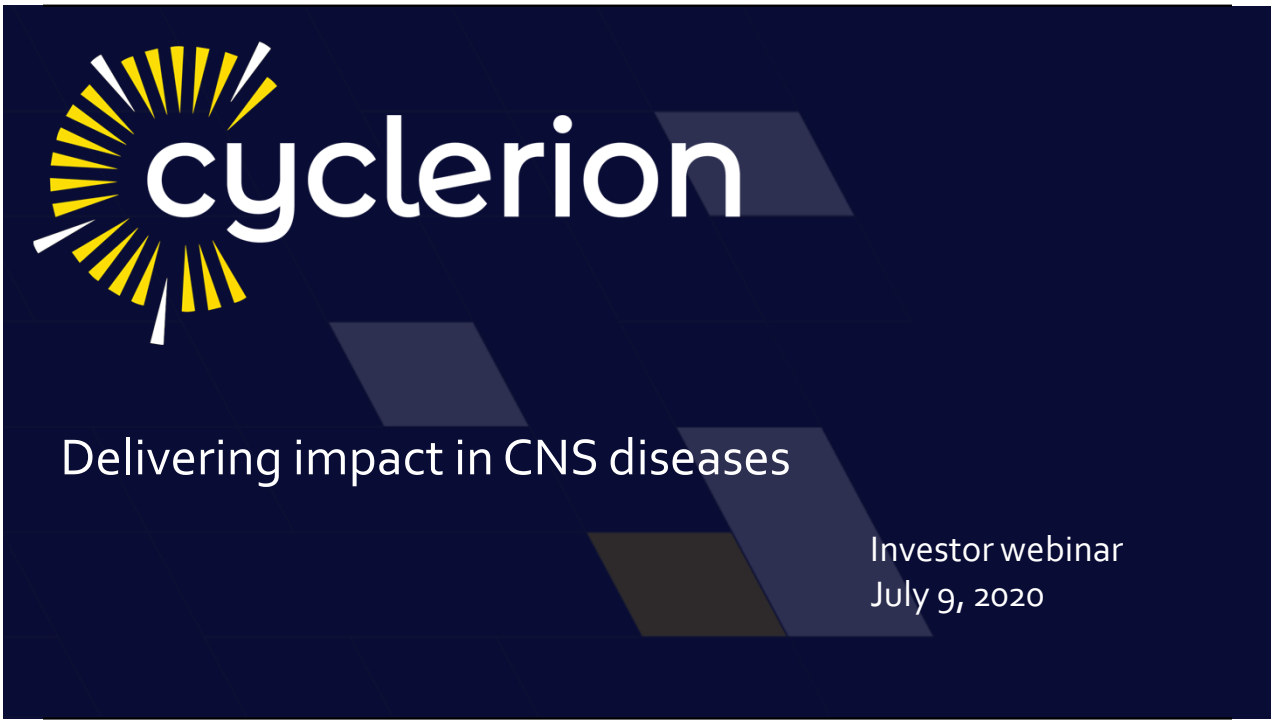
Finally, there are clinical consensus guidelines from the American Heart Association and the Vas-Cog Society for making diagnosis and for treatment recommendation. So I think we can recognize patients with vascular changes and then the prevalence is about 30% among persons with Alzheimer's disease. I'm quite confident that that part can be accomplished readily. And then in terms of the promise for the therapy, well, we don't have any disease modifying therapies for vascular dementia or mixed vascular and Alzheimer's disease. So there's a huge unmet need. We do treat them with conventional care and vascular risk reduction, controlling blood pressure, treating diabetes, recommending cessation of smoking, all the standard things we do to target the vascular system. But I can tell you from experience and also from the published literature, that these patients still develop progressive small vessel disease despite conventional vascular risk management.

**Dr. Eric Smith (01:15:11):**

This has been seen in most stroke studies, for example, where you see a continued accrual of white matter lesions despite treatment with ACE or ARB or calcium channel blockers. I think both in my own experience, as well as the literature, we see that the current pharmacological options are not sufficient. Further, we know that the patients with progressive lesions do worse cognitively and continue to decline and get worse from their dementia. So to me, I think this is a very promising pathway, but I'll turn it over to Chris to see if he has any additional thoughts or comments along the line to that question.

**Chris Wright (01:15:50):**

Sure. No, I think you covered that very thoroughly. I guess the one thing I might add is that, although we are focused on this targeted population and enriching for specific vascular pathology and other elements, it's certainly possible that the therapy, if it's effective in that context, may also be beneficial to patients that have Alzheimer's disease alone, to the degree that that exists without some vascular aspects, or with vascular dementia alone. So I think the concept is finding the right population to start with, to optimize our likelihood of success. Then if we see something there, I think that it's very likely that there's other patients outside of that small circle that will benefit, that could be determined in longer and later stage studies.




**Peter Hecht (01:16:52):**

Great. Thanks to you both for taking the questions, and we're out of time. So let me thank you all again for accommodating the early start and for joining us this morning. The content, both the slides and, if not already very shortly, the audio feed should be available on the Cyclerion website on the investor relations subset of the website. As always, we're available to answer questions and follow up one-on-one offline. We're available at any time. So thank you very much for your attention this morning, and thanks to all the participants. Have a great day and stay safe.

# Citations

| Page | Topic | Citation |
|---|---|---|
| 25 | MELAS epidemiolgy | Sources: 1. J Neurol. 2016; 263: 179–191; US population estimated at 327.2 million;2. Brain. 2003; 126(5): 1231–1240; 3. NIH Genetics Home Reference; 4. NCBI GeneReviews; 5. Neurotherapeutics. 2013 Apr; 10(2): 186–198 |
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