DITCHING DELAY: GH001'S INSTANT IMPACT ON DEPRESSION

Connor Williams
Senior Research Analyst
RTW Investments, LP

Velichka Valcheva, MD, MSc
Chief Executive Officer
GH Research

Ditching delay: GH001's instant impact on depression

Connor Williams: Welcome to The RTW Podcast. I'm today's host, Connor Williams, Senior Research Analyst at RTW, responsible for research in neurological disease. Today I'm speaking with esteemed industry colleague, Dr. Villy Valcheva, CEO of GH Research, a cutting-edge biotech company advancing therapies for psychiatric and neurological disorders.

You wouldn't normally find me in RTW's podcast studio, but there's quite a bit going on in neuropsych that's worth talking about. I recently had a conversation with our Chief Business Officer, Stephanie Sirota, about the emergence of psychedelics as a transformative therapy for treatment-resistant depression.

And now I have the privilege of speaking to Dr. Valcheva, an industry leader with more than 20 years of leadership experience in the pharmaceutical and biotech industries, including companies such as Albireo, Ipsen, and Sanofi. Villy, thank you for joining us today.

Dr. Velichka Valcheva: Great to be here, Connor. I'm really excited about this.

About GH Research

Connor Williams: Let's begin with GH Research. What is GH Research, and what's the main problem you're trying to solve?

Dr. Velichka Valcheva: GH Research is a biotech company. We're headquartered in Dublin, Ireland. We are developing a treatment for mental diseases, and our value proposition is that it will be practice-changing treatment that would lead to ultra-rapid remission, which can be sustained with infrequent administrations.

Dr. Velichka Valcheva: Patients with depression nowadays suffer insurmountably. They have years of depressive symptoms without any treatments that could lead to remission. Usually takes oral antidepressants four to six weeks to work, and there's a very low percentage of patients that get any remission. We're developing a new treatment, GH001, that could lead to improvement in the depressive symptoms even on the same day of the treatment. And then it's sustained months and months with infrequent administrations.

Connor Williams: I know you said you're treating depression, but it's specifically treatment-resistant depression. What's the difference between that and maybe run-of-the-mill depression that you might first treat with an SSRI?

Dr. Velichka Valcheva: So patients with treatment-resistant depression would have multiple major depressive episodes. They would be treated with at least two prior treatments that would've been taken in the appropriate dose and would be ineffective for weeks.

These patients, with time, become resistant to any antidepressive treatments, and it's hard to find a new treatment. So they could suffer for years before anything works. So that's the treatment-resistant depression.

There's a high unmet need, and believe it or not, there's millions of patients out there in need of new treatment.

Connor Williams: Right—three million patients in the U.S. with treatment-resistant depression.

Dr. Velichka Valcheva: Yes, correct.

Connor Williams: I know standard of care is Spravato. How do you think about Spravato, particularly as it compares to your therapy that you're developing?

Dr. Velichka Valcheva: Yes, Spravato is currently the benchmark. It gained approval a few years ago. The difference between Spravato and us is that Spravato has a very complex induction system, where you need to give it twice a week for four weeks and then once a week for four more weeks.

It takes time for patients to feel the benefit and go in remission. With GH001, which is our treatment, patients are treated once. On the same day they already see benefit, which our Phase 2b data showed. And that sustained with a lot less treatments, on average four treatments for six months.

Connor Williams: How long would a treatment visit last?

Dr. Velichka Valcheva: With GH001, one day in the interventional psychiatry clinic should be around one to three hours. There is one hour observation period, after which patients are ready to go home.

Connor Williams: How long do you think patients can go between doses of GH001?

Dr. Velichka Valcheva: We foresee that there will be infrequent treatment visits, so maybe on average four treatments in six months.

We are still in phase 2B. We are planning for a pivotal program. The pivotal program will show us a lot more for the future of the treatment. I guess as well, something else that happens is when a treatment is in the market and it's available to physicians, with time they learn how to use it, and it all optimizes the treatment regimen.

Becoming CEO of GH Research

Connor Williams: What was compelling about GH that attracted you to work at GH, and what do you think is the biggest potential risk?

Dr. Velichka Valcheva: I was the chief medical officer in the company when the board offered me to become the CEO.

"I'll never forget that day. We were on holiday, and I told my husband, 'You know, I might become the CEO of my company,' and he said, 'No, no, no, no, no, no, no.'"

I am extremely lucky to have a very supportive husband. We've been married 30 years now and he knows that I'm an ambitious woman, so he's been very supportive with me becoming a CEO.

Why did I take the job? You know, being the Chief Medical Officer, I was deeply involved in the phase 2B conduct. And I already knew that this is a once-in-a-lifetime opportunity to change the treatment paradigm of such a big disease. As much as it sounds a cliché, I thought becoming the CEO of the company gives me the ability to hold the destiny of this drug in our own hands rather than entrust it in somebody that would come from outside.

So I've got a great team at GH. I've got a fantastic drug that we all know now that it works, based on the Phase 2B data. I guess the biggest challenge is not to mess it up. And it's all about the execution. I am a very much execution type of person, so it also made me think perhaps I'm the right person for this particular treatment, for this particular company.

And that's how I took the job.

Connor Williams: And maybe even before that, there was a time where you were researching what 5 Methoxy DMT was. I guess what were your first thoughts? Because 5 Methoxy DMT, it's not exactly a regular molecule you come across every day.

Dr. Velichka Valcheva: When I read about 5-MeO-DMT and GH Research I thought, "You know, that's a challenge worth taking," because, come on, everyone has a relative or a friend that have been depressed. And there is complexity around psychedelics, but it's not something I'm not able to face. So these were my thoughts: maybe complex but more exciting, and definitely worth taking on as a challenge.

The difference between GH001 and other psychedelics

Connor Williams: What do you think makes GH001 different from other treatments in development for treatment-resistant depression?

Dr. Velichka Valcheva: If you're a depressed patient, struggle through many years, can't enjoy life, can't enjoy time with your family, you can't go to work, you want something to work quickly, right?

You don't want to wait for weeks and be exposed to multiple side effects before you get some benefit, if any. And the difference with GH001 is that you go to the clinic, it's a visit of one to three hours, you do inhalation, which could be one to three inhalations depending on what dose you need. And after that there's improvement in your depressive symptoms two hours later. That I think is the number-one difference. The second difference is that oral antidepressants you take every day, and you suffer from the multiple side effects they have.

Spravato has this complex regimen. You know, patients could be drowsy. Even on the next day, they can't drive. They need to be driven home. With GH001, usually the side effects are mild to moderate. They're around the psychoactive phase. And 97.4% of the patients in our phase 2B trial were discharge-ready one hour within the last dose. And there was no sedation and no dissociation at discharge.

You also have the convenience of infrequent re-treatments. And four times on average in six months is really doable, compared to everything else that you need to either take every day or twice a week or once a week.

A lot of the psychedelics are developed with mandated psychotherapy. Our program is without mandated psychotherapy, which brings simplicity.

When you go to the clinic you're administered and you can go home. There is no necessity to have psychotherapy sessions which improves the cost, the scalability in the commercial model, and gives the patient choice.

Connor Williams: I've said it before that I find it to be a really compelling data set, and I think it is the best treatment-resistant depression data at least I've ever seen in my life. I can't think of another study that's any better. And the delta is 15 points on the MADRS scale, placebo-adjusted. Could you help us understand what the treatment effect was to patients and how it compares to standard of care?

Dr. Velichka Valcheva: First, just to say it's 15.5 points, okay? (LAUGH). Just making sure we sweat a lot for this data and—

Connor Williams: For other companies half a point would mean a lot, and it would be most of their effect size. I remember when we were in our office on the Friday before the data came out, me, Rod, and Gotham were betting what the placebo-adjusted delta would be.

I was saying I would be happy with anything north of seven. And Gotham was saying he thinks it would be closer to nine or ten.

When you first showed us the data, and it was a 15-point delta, I remember being more shocked than I've ever been in my life because it's incredible, but to anyone that doesn't know what a 15.5-point MADRS delta is, what does that mean?

Dr. Velichka Valcheva: Even on the day of administration, already when patients come out of the treatment room, they say that they can put tasks into problems. They can cope with the complexity of life—which was a massive burden because of the depression—better.

They can do things one by one and start enjoying life. So patients might want a nice meal or a nice cappuccino, go to a café, or go to the movies with their family. And to you and me that might sound trivial, right?

Okay, we can just go to the movies. But depressed patients, they lose the ability to enjoy life and to participate in life. They don't have friends. Their family is usually staying away from them. They lose their jobs or they're not efficient. So a reduction of MADRS of 15 is a tremendous improvement in somebody's way of how they feel and how they enjoy life.

Connor Williams: If I'm remembering, Spravato's remission rate is at 20% and you guys had north of 50%?

Dr. Velichka Valcheva: So Spravato remission rate with their monotherapy, that is their most recent data at day 28, which is their primary endpoint, is 21%.

And our remission rate is 57.5% on day eight. First you see it on the same day or in the first week, the change in the patient.

Even the neighbor notices it. And with Spravato, it's gradual and you never reach these high levels of remission like with GH001.

Connor Williams: Right. I still think about people I know telling me that the data had to be fake because the placebo was too low. I'm like, "What do you want? The placebo can't be 10 or you'll be upset, but if the placebo's less than five you're still upset?" Insanity.

Dr. Velichka Valcheva: Human nature.

Connor Williams: Human nature, right.

Dr. Velichka Valcheva: But a lot of the top KOLs (key opinion leaders) think this is our biggest achievement. It provoked this wave of KOLs that now are writing up papers and guidance on how to manage functional non-blinding in order to support us with the FDA. So they're actually talking on our behalf to the FDA for the measures to address functional non-blinding so it doesn't become a hurdle.

The difficulties of developing a scheduled substance

Connor Williams: Obviously, 5 Methoxy DMT is a scheduled substance in the United States. Could you maybe talk about the difficulties of developing and running trials with the scheduled substance?

Dr. Velichka Valcheva: Very important point and learning from the phase 2B is planning.

Because you need to get these controlled drug licenses for the sites, and every new trial, every new drug, you need to get a separate license, that takes time.

So it's important to plan and to take into consideration the U.S. regulations but also each state because it could differ by state. Then there's also rules on how to manufacture, how to distribute, and how to store the drug on site.

There's multiple rules and regulations that we need to observe. And now that we've completed a large trial with 80 patients in more than 20 sites, we've got the know-how to do it.

Dealing with the stigma of psychedelics

Connor Williams: Exciting. 5 Methoxy DMT is a psychedelic, and there's obviously a lot of stigma.

How do you deal with that while developing it as a serious medicine to help patients with an unmet need?

Dr. Velichka Valcheva: It's changing. You know, there are countries where it's a lot easier now to develop psychedelics, such as Australia, the Netherlands, and some of the states here.
How do we do it?

"Media needs to stay away from these stories that could lead to stigma but rather focus on the positive results, such as our data and the fact that psychedelics can change the treatment paradigm of mental diseases, not just depression but PTSD, anxiety, and many others."

So it's a combined effort between us biotechs, and we need to always present the positive data that we generate.

But also, the media should divert their focus from sensations and focus on the positive data, which would destigmatize psychedelics.

Connor Williams: I know there's often a lot of media arguing that they're not safe. I guess with your compound, 5 Methoxy DMT, what gives you confidence that this compound is safe to give to the masses of people who have TRD and need another option?

Dr. Velichka Valcheva: Well, our compound is synthetically manufactured in GMP facilities. And we derive pure 5-MeO-DMT. We know exactly what dose we are delivering to the patient.

We're delivering GH001 in a safe clinical setting, and it will be one day in the interventional psychiatry clinics.

And the phase 2B data shows that we've got no serious adverse events in our double-blind data that we presented and that most of the adverse events that patients see are mild to moderate, such as headache, nausea, and others that subside around the psychoactive phase. It's important to differentiate retreat and being a severely depressed patient going to the clinic for treatment. There's a big difference.

Connor Williams: Can you explain the drawbacks of paradigms that use psychotherapy in combination with a psychedelic?

Dr. Velichka Valcheva: Therapies developed with psychotherapy have a few hurdles to overcome. The FDA and other regulators don't regulate psychotherapy.

Number two would be cost because psychotherapy adds to the cost of the overall treatment. And added to that is the convenience because, when you go to an interventional psychiatry clinic, you need to factor in the cost of psychotherapies, the time, which would bring a different commercial model compared to what we have.

Connor Williams: Obviously, you guys have presented really impressive data recently, but what are you most proud of during your time at GH? What really fulfills you about the job?

Dr. Velichka Valcheva: What fulfills me is success. That is what drives me the most. And it's not success driven by my own ego. Every little success makes me extremely proud. It's success with the data.

But it's the success in the BD and PPD trials as well, which were very positive. Developing our own device, every single step we take towards making this drug available makes me proud and happy.

What else can GH001 treat?

Connor Williams: Yes, the bipolar data as well as the postpartum, that maybe touches on something interesting in psychiatry. What other indications, aside from treatment-resistant depression, do you think that a molecule like 5 Methoxy DMT could be purposed for?

Dr. Velichka Valcheva: We've got a long list of different indications that we've been approached by the scientific community, academic centers, KOLs that definitely see GH001 would work. We have the proof of concept in postpartum depression and bipolar disorder too. These are two conditions with very high unmet need.

We also see from our phase 2B data that GH001 works really well in anxiety. PTSD, for example, is another condition. Patients with terminal end-stage cancer as well could be another area. Uncurable pain, chronic pain. That's the good thing about GH001—that once we develop it for TRD, then we can expand on other indications.

Connor Williams: I actually do have a question now, and I'm genuinely curious because I don't know the answer. You know, 5 Methoxy DMT, it got its international non-proprietary name.

Dr. Velichka Valcheva: Mebufotenin—

Connor Williams: Okay. How do you pronounce that? I've been trying to figure it out—

Dr. Velichka Valcheva: Mebufotenin.

Connor Williams: Mebufotenin?

Dr. Velichka Valcheva: Yes.

Connor Williams: Internally at GH, obviously you refer to your program as GH001, but when you have to refer to the compound has Meb—

Dr. Velichka Valcheva: Mebufotenin—

Connor Williams: —Mebufotenin taken over yet or is it still 5 Methoxy DMT?

Dr. Velichka Valcheva: We've developed our formulation. It's proprietary. We have the device. So we refer to it as GH001 or Mebufotenin.

Connor Williams: Okay. I like it. I'm going to practice that a whole bunch more and maybe I'll come back and be able to pronounce it next time I—

Dr. Velichka Valcheva: It's the bufo!

Connor Williams: Oh. Oh, that makes sense, the frog, Yes.

Dr. Velichka Valcheva: Mebufotenin.
I don't know if it's related to the frog, but it definitely makes it easier for you to say it.

The future of GH Research

Connor Williams: In terms of GH's trajectory, where do you see the company going in the future?

Dr. Velichka Valcheva: Our focus is to overcome the hurdles in the U.S. and have a global pivotal program, and then develop the treatment for TRD, look at other indications, and expand into other mental diseases. That's my goal. I think GH has the opportunity to become a big player.

Connor Williams: We absolutely agree. Your product GH001, which is 5 Methoxy DMT, is derived from a frog that you can find particularly in the Sonoran Desert. Have you ever seen one of the frogs in real life?

Dr. Velichka Valcheva: So I was at ACNP last year in Arizona, and you're going to find it very funny, but I did go to look for a toad. One of the KOLs told me that in order to see a toad it needs to rain, and it didn't rain for a long time in Arizona. So, no, I haven't seen a real toad. But I can tell you that we manufacture GH001 synthetically in GMP facilities. And there are no toads involved in the—

Connor Williams: No toads—

Dr. Velichka Valcheva: —manufacturing —

Connor Williams: —farms in the future of GH.

Dr. Velichka Valcheva: No, no, no, no.

Connor Williams: Apparently you have to startle the toads to get the secretion of bufotoxin. Do you know exactly how they scare the toads?

Dr. Velichka Valcheva: To be honest, I don't know how exactly it's done. If you want to join me, you and I can go look for a toad and gently startle it, and then we can leave the audience on a cliffhanger because next time you and I meet we can tell them what happened.

Connor Williams: Okay. I love this. Maybe shifting gears to talk about you.

What do you attribute your success to? What type of leader are you? And do you have any advice for young people who see you as a role model, particularly young women in the industry?

Dr. Velichka Valcheva: Since I was a kid, I've always been very ambitious. And I always strived for success. I'm also a very positive person and an extrovert. I love to engage with people externally. And the CEO role actually allowed me to expand on my areas of engagement—not just KOLs but I now engage with Wall Street and investors, engage with media.

And it's something that I really, really enjoy because it allows me to spread the positive side of the development and the accomplishments we have with GH001.

As a leader, I like to deconstruct complexity and make it simple and then have a crystal-clear vision that I communicate to people.

The CEO job is not for the faint-hearted. It's really busy. There's a lot of commitment required. You need to be very careful to keep your balance because you can easily just only work and do nothing else. And you need to enjoy it.

What I say to my team is, "I will do everything to inspire you and to bring you forward on our mission, but you need to be happy with what you do. You need to enjoy the ride as long as it goes and be happy with our mission."

I guess that's who I am as a leader—very open, very transparent.

One of my favorite things is to have young people on the team and see them evolve.

And I just wanted to say, believe in yourself but then live in the today. And also, super, super important—be ambitious and never be mediocre. That's the road to success.

Connor Williams: Villy, thanks so much for speaking with us today and giving me more airtime on one of my favorite subjects.

Dr. Velichka Valcheva: Pleasure, Connor.

Statements reflect RTW's views and opinions as of the date hereof and not as of any future date. All expressions of opinion are subject to change without notice and are not intended to be a forecast of future events or results.

The views expressed by guests are their own and their appearance on the program does not imply an endorsement of them or any entity they represent.

rtw

CONTACT US FOR FURTHER INQUIRIES

RTW Investments, LP
40 10th Avenue, Floor 7
New York, NY 10014
(646) 597-6980

Find more information at:
rtwfunds.com