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PRESENTATION

Amin Makarem - *Jefferies LLC - Equity Analyst*

Hello, everyone. Thanks for being here. I'm Amin Makarem, one of the biotech analysts here at Jefferies.

I'm happy to introduce and welcome Shao-Lee Lin, CEO of Cue Biopharma.

This is a standard presentation format, and with that, I'll hand it over to Shao.

Shao-Lee Lin - *Cue Biopharma Inc - President, Chief Executive Officer, Director*

Thank you so much for the introduction, Amin, and thanks to Jefferies, for the opportunity to present at your conference. Here are our forward-looking statements, which I'm sure you'll all study. It is an incredibly exciting time for us at Cue.

Over the past year, I've been actively drug hunting for transformational therapies alongside a small and highly experienced team. Throughout my career, both in big pharma and smaller biotech, I found that among many promising programs that one might find in a given year, only one or two actually have the potential to fundamentally change outcomes for patients.

When we began this process, we were looking for programs supported by compelling biology, differentiated mechanisms, and the potential to address significant unmet medical needs. That search led us to both CUE-221 and CUE-401.

While these are distinct programs, they are connected by a common scientific construct that I like to describe as precision immuno-engineering, the deliberate design of therapies to modulate the immune system in biologically informed ways. This approach is central to both programs and created the opportunity for us to form a cohesive portfolio with the potential to impact patients across both allergic as well as autoimmune diseases.

CUE-221 is a novel anti-IgE molecule that has a dual mechanism of action, and is currently being evaluated in a Phase 2 study in chronic spontaneous urticaria, or CSU. We will discuss both the unique characteristics of the molecule and the ongoing and planned trials in greater detail later in this presentation.

CUE-401 is a first-in-class bifunctional cytokine that targets both IL-2 and TGF-beta in a single molecule. The program is built on the shoulders of Nobel Prize-winning discoveries that highlighted the critical role of regulatory T-cells in maintaining immune tolerance and controlling autoimmune disease.

By combining these two powerful biological pathways, CUE-401 is designed to harness and enhance regulatory T-cell function to restore immune balance. It is advancing toward Phase I clinical development in autoimmune disease.

We have multiple significant milestones expected over the second-half of this year.

We plan to submit IND applications for both programs. For CUE-221, we expect to see results from the ongoing Phase 2 CSU study in the second-half of this year. These data will further inform our next studies, including a Phase 2b study in food allergy, which I will discuss later in the presentation.

For CUE-401, we expect to initiate a first-in-human Phase 1 study by end of year. Alongside the strategic combination to create this immunology-focused and clinical-stage portfolio, we also completed a financing in parallel, which enables cash runway through our key milestones and includes potential for significant value inflection for the company.

The combination further assembles a highly complementary team with deep expertise across drug discovery, clinical development, and immunology.

Together, this team is well positioned to support the acceleration of the portfolio and our evolution as a clinical-stage company.

This is our portfolio at a glance. As I mentioned already, our two most advanced programs represented at the top are CUE-221 and CUE-401, which are the focus of this presentation. We also have partnerships around CUE-501, a B cell depleter licensed to Boehringer Ingelheim, and the CUE-100 series, which targets multiple solid tumors and is licensed to ImmunoScape. Both of these programs also offer potential for milestone payments.

Next, some detail on the portfolio starting with CUE-221. This slide summarizes the highlights of CUE-221, a novel dual-mechanism-of-action anti-IgE therapy with potential across multiple allergic diseases. At its core, this is a functionally distinct novel anti-IgE antibody developed by the innovators of omalizumab but engineered with a differentiated dual mechanism of action.

Importantly, the antibody not only neutralizes free IgE with high potency, but also downregulates new IgE production, a combination we believe could translate into deeper and more durable disease control.

What gives us confidence is the consistency of the data we've seen to date. Across preclinical and clinical studies, we've observed robust and durable IgE suppression, clinically meaningful efficacy signals in CSU and a favorable safety and tolerability profile.

The ongoing Phase 2 CSU study being conducted in China is designed to benchmark efficacy directly against omalizumab while also helping define the optimal dosing strategy for future studies. We expect this study to read out in the second-half of 2026.

We are now entering the next major phase of value creation for the program. We have selected food allergy as our lead indication because of the significant unmet medical need and the central role that IgE plays in driving disease biology, making it an especially compelling setting to demonstrate the potential for CUE-221.

Food allergy is a growing public health problem. In the US alone, there are over 30 million Americans affected, and the incidence of severe allergic reactions continues to rise. In fact, anaphylactic food reactions increased by nearly 400% in the last decade.

The burden on patients can be substantial. More than half of adults and over 40% of children with food allergy are expected to experience a severe reaction during their lifetime, including the potential for life-threatening anaphylaxis.

Importantly, anti-IgE therapies represent a clinically and commercially validated market. As shown in the figures at the bottom of the slide, Xolair was the first anti-IgE therapy approved for food allergy in 2024.

The strong sales growth shown on the left-hand figure, together with the rapidly increasing number of treated patients shown in the right-hand figure, demonstrate strong physician adoption and significant patient demand.

Omalizumab has clearly established that targeting IgE can be effective across allergic diseases. However, there remains high unmet need across these diseases, and especially in patients with high baseline IgE levels, which is common in food allergy.

Clinical experience has shown that meaningful patient benefit is achieved when free IgE levels are reduced to approximately 50 ng/mL or below, with optimal outcomes often observed when free IgE approaches 25 ng/mL. Achieving and maintaining these target IgE levels is critical for maximizing clinical benefit. These IgE thresholds form the basis for the approved omalizumab dosing tables in food allergy. To achieve adequate IgE suppression, dosing must be individualized according to both patient weight and baseline IgE levels. This results in a significant treatment burden, including frequent dosing up to every other week and multiple injections for many patients.

Furthermore, patients with high IgE levels above the dosing tables are not eligible for treatment.

On the horizon, we observe that emerging anti-IgE therapies appear to offer primarily incremental improvements by extending half-life and improving convenience, while others are exploring novel mechanisms that remain at an early stage of clinical validation.

Omalizumab has demonstrated that targeting IgE can provide meaningful clinical benefit across a broad range of allergic diseases, and we believe CUE-221 has the potential to address these same indications. While food allergy represents an attractive initial indication because the disease biology is highly dependent on IgE, there are numerous other diseases where IgE plays an important pathogenic role, including chronic spontaneous urticaria, atopic dermatitis, and allergic asthma.

We believe there is a significant opportunity for a novel anti-IgE therapy that can more completely and consistently suppress and therefore optimize free IgE levels, while maintaining a favorable safety and convenience profile.

This slide summarizes the molecular design features that we believe position CUE-221 as a novel anti-IgE therapy. Importantly, CUE-221 was developed by the makers of omalizumab. A decade later, this pioneer team designed the murine precursor of CUE-221, a biologically differentiated novel anti-IgE.

The molecule has higher binding affinity in the picomolar range and a slower dissociation or off-rate compared to omalizumab. Together, these properties support stronger and more sustained engagement of the target.

To better understand the differentiated mechanism of CUE-221, it's helpful to first review the biology of IgE. IgE interacts with two key receptors.

The first is the high-affinity receptor, or FcεRI, shown on the left-hand side of the slide. This receptor is expressed on mast cells and basophils and eosinophils. When IgE binds to the high-affinity receptor and is cross-linked by an allergen, it triggers cell activation and degranulation, leading to the allergic responses we recognize clinically, including severe reactions such as anaphylaxis. As a result, this is the pathway that most anti-IgE therapies are designed to block.

The second receptor is the low-affinity receptor, or FcεRII, also known as CD23, shown on the right side of the slide. The low-affinity receptor plays an important regulatory role in IgE biology. Under conditions of elevated IgE, signaling through the low-affinity receptor acts as a natural negative feedback mechanism that helps suppress further production of new IgE.

In other words, CUE-221 not only pulls out the stopper to drain the bathtub, but also allows turning off of the spigot which fills the bathtub.

This slide highlights one of the key mechanistic differences that distinguishes CUE-221 from existing anti-IgE therapies.

As we discussed on the previous slide, IgE interacts with both the high-affinity receptor and the low-affinity receptor, CD23. Omalizumab blocks IgE interactions with both the high-affinity and low-affinity receptors. In contrast, CUE-221 is specifically designed to block binding to the high-affinity receptor while preserving IgE engagement with CD23.

As shown on this slide, CUE-221 maintains the interaction between IgE and CD23, whereas omalizumab does not and remains inert. We believe this is an important distinction because it enables CUE-221 to inhibit the pathway responsible for allergic reactions while preserving a natural regulatory mechanism involved in down-regulating new IgE synthesis.

In this experiment, human cells were stimulated to produce new IgE synthesis. Treatment with CUE-221 still allows even drug-bound IgE to bind to CD23 and engage the negative feedback to downregulate new IgE synthesis, resulting in markedly less IgE mRNA expression, shown on the left, and IgE protein production, shown on the right.

In contrast, omalizumab has a limited effect on IgE mRNA expression or new IgE synthesis. Importantly, these findings provide a biologically plausible rationale for what we have observed in the clinic, which we will discuss on the following slide.

Here are the main results from the Phase 1 Single Ascending Dose study in patients with CSU. The line in yellow represents CUE-221 drug concentration, which rises with increasing doses up through 10 mg/kg. The orange line represents urticaria clinical response scores, where we observed improvements in clinical symptom scores in a dose-dependent fashion.

In purple is free IgE and here is where I want you to focus. What we see is that all subjects treated with CUE-221 achieved free IgE levels below the lower limit of quantification, in this instance, 24 ng/mL, by the first measurement at week one.

A single 2 mg/kg dose, highlighted in the upper right-hand corner, maintained free IgE suppression for at least one month, while single doses greater than 2 mg/kg sustain suppression for more than three months. We believe this level of rapid and durable suppression is unique to CUE-221.

This slide outlines the ongoing Phase 2 CSU study being conducted in China by our partner's related entity, which we view as an important upcoming value inflection point for the program. Study enrollment is complete, with 145 patients randomized across three CUE-221 dose groups, along with a placebo and an active omalizumab comparator arm. Patients are treated for up to 16 weeks, with follow-up extending through week 36.

Importantly, the study is designed not only to evaluate efficacy versus placebo but also to directly benchmark performance against the current anti-IgE standard of care.

The primary endpoint is complete hive symptom score, defined as HSS7 of 0, or no hives, at week 12. This represents a high efficacy bar in CSU. We expect data from this study in the second half of this year, 2026, and we believe the results will provide important insight into both the efficacy profile and the optimal dosing strategy as we prepare for upcoming global Phase 2b studies.

And now moving into detail on CUE-401. This next program represents a potential first-in-class bifunctional cytokine designed to restore immune tolerance in autoimmune disease. CUE-401 combines affinity-attenuated IL-2 and TGF-beta signaling within a single fusion protein. As such, it delivers two key pathways known to support the induction and expansion of regulatory T cells, or Tregs.

Importantly, CUE-401 was engineered to enhance selectivity through attenuated TGF-beta activity and preferential signaling through IL-2 receptor-expressing cells, with the goal of improving specificity and reducing off-target effects.

While attenuated IL-2 approaches have been successfully developed and validated clinically, CUE-401 represents, to our knowledge, the most advanced therapeutic to combine both attenuated IL-2 and attenuated TGF-beta signaling within a single molecule. This unique design creates an opportunity to evaluate this dual cytokine agonism for the first time in humans.

To date, the program has generated robust in vivo proof of mechanism and efficacy data across multiple immune-mediated disease models. Operationally, the program is advancing toward the clinic as well, which we will discuss later.

Overall, we believe CUE-401 has the potential to address a broad range of autoimmune diseases by restoring immune regulation rather than broadly suppressing immunity.

The importance of Tregs in controlling autoimmunity and maintaining immune homeostasis has gained increasing recognition across the scientific community.

In 2025, the Nobel Prize in Physiology or Medicine highlighted foundational discoveries that established the critical role of FOXP3-positive regulatory T cells in keeping immune system balance.

More recently, a publication in Nature from a leading scientific laboratory provided additional external validation for the concept of simultaneously engaging both the IL-2 and TGF-beta signaling pathways. The study utilized a tool molecule designed to activate both pathways and demonstrated encouraging effects on regulatory T cell biology, further supporting the potential of this dual-signal approach.

Together, these developments reinforce both the growing excitement around Treg-directed therapies and the scientific rationale underlying CUE-401. The design of CUE-401 is shown in the figure on the right. The molecule consists of an affinity-attenuated IL-2 domain on an Fc backbone paired with an attenuated TGF-beta domain integrated into a single construct.

By attenuating both signaling components, CUE-401 is designed to limit signaling through either pathway alone while enabling coordinated engagement when both receptors are present on the same target cell.

Our goal is to deliver the combined signals required to selectively promote regulatory T cell biology, including both the expansion of naturally occurring Tregs and the conversion of conventional T cells into inducible FOXP3+ induced regulatory T cells.

Importantly, we generated encouraging efficacy data across multiple preclinical models, which we will highlight here. In this experiment, we investigated whether coordinated signaling through both the IL-2 and TGF-beta pathways is required to drive the induction and expansion of FOXP3+ regulatory T cells.

What you're looking at is the activity of the individual components of CUE-401 compared with the fully intact molecule. When the attenuated IL-2 component or the attenuated TGF-beta components are evaluated on their own, we see little to no meaningful expansion of the FOXP3+ population.

In contrast, when both components are combined within the fully intact CUE-401 molecule, there is a clear synergistic increase in proliferating FOXP3+ regulatory T cells. This is exactly the outcome we would hope to see based on the way CUE-401 was engineered, providing functional evidence that the dual-signal approach is driving the desired Treg response.

The next set of data demonstrates the activity of CUE-401 across multiple preclinical models of autoimmune disease.

As shown here, CUE-401 consistently produced evidence of disease attenuation in autoimmune gastritis on the left, experimental autoimmune encephalomyelitis or EAE in the middle, and graft-versus-host disease or GvHD on the right. Across these models, we observed preservation of tissue architecture in histology, delayed disease onset, and in certain cases, improved survival.

The GvHD model is particularly noteworthy. In this setting, wild-type IL-2 alone has been reported to worsen disease. In contrast, CUE-401 not only delayed disease progression, but also improved overall survival, highlighting the potential impact of the molecule's differentiated design.

On the right, we see the expected immunologic consequences of engaging these pathways, with broad suppression of pro-inflammatory cytokines including IL-17, GM-CSF, interferon-gamma, and TNF-alpha. These findings are consistent with the generation of a more tolerogenic immune environment and support the proposed mechanism of action.

Together, the in vitro and in vivo data generated to date provide encouraging evidence that CUE-401 is producing the intended biological effects and support continued clinical development of the program.

This slide outlines the proposed first-in-human Phase 1 study for CUE-401. Overall, this is a relatively standard Phase 1 design. We intend to proceed thoughtfully, given the potential for a narrow therapeutic window.

The study includes both SAD and MAD portions, with the flexibility to interpolate between the SAD and MAD cohorts as safety data emerges. The program would ultimately expand into a patient cohort to begin evaluating biological activity in a patient population.

In summary, we are advancing an enhanced, clinical-stage pipeline of potentially transformative therapies with CUE-221 and CUE-401. Therapies that we believe could offer the concept of functional cures across allergic and autoimmune diseases.

As I discussed, we have multiple milestones that are near-term. And we are well-positioned for significant value inflection and funding projected to cover our milestones along with the creation of a complementary team to support our strategic acceleration into a clinical stage immunology company. Thank you for your attention.

Amin Makarem - *Jefferies LLC - Equity Analyst*

Thank you very much. Thanks for the audience.
