

John Celebi – Chief Executive Officer, Egle Therapeutics (00:01):

Good afternoon, and thank you all for joining us. I'm John Celebi, CEO of Egle Therapeutics. As a reminder, today's webcast has been pre-recorded. Following a data presentation, we will have a discussion session. Atopic dermatitis is one of the most common chronic inflammatory diseases in the world, and the past decade has transformed how we treat it. Biologics and JAK inhibitors have given many patients real relief, but most of these therapies work by blocking a single pathway. And for many patients, the disease returns once treatment stops. That leads to the question at the center of today's discussion. Can we move from suppressing inflammation to restoring the immune system's own ability to control it? That is the question that Egle was built to answer. Our work focuses on regulatory T-cells, the cells whose job it is to keep immune responses in balance. Our lead program, EGL-003, is an engineered IL-2 designed to preferentially expand and activate regulatory T cells.

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In phase one, EGL-003 produced substantial and durable expansion of regulatory T cells, including skin homing populations and was well tolerated across cohorts. We are now initiating a placebo controlled multi-dose study in patients with atopic dermatitis. Let me briefly introduce my colleagues from Egle who are with us today. Dr. Kenji Hashimoto, our chief medical officer, leads our clinical development teams at Egle and has led multiple large clinical programs across the industry. Dr. Jonathan Back is a director for autoimmunity and our scientific program lead for EGL-003 program, and has led multiple autoimmunity programs spanning drug discovery through early clinical development. They will present the scientific and medical data for EGL-003 and join us for a discussion at the end. Now to our guest, I can't think of anyone better placed to guide and remark on this conversation than Professor Stephan Weidinger. Professor Weidinger is professor and chair for dermatology at the Christian-Albrechts University and director of the Department of Dermatology and Allergy at the University Hospital Schleswig-Holstein in Kiel, Germany, where he oversees the Center for Inflammatory Skin Diseases.

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He trained in medicine at the University of Regensburg and earned his MD and PhD at the Technical University of Munich, where he went on to lead the inflammatory skin disease unit. His research on the molecular mechanisms and treatment of atopic dermatitis has shaped how our field understands the disease, its genetics, its biology, and why patients can respond differently to the same therapy. He coordinates BioMAP, the International Consortium on Biomarkers in Atopic Dermatitis and Psoriasis. He leads Treat Germany, the National Registry tracking how patients actually fare on systemic treatments in everyday practice. He's also a principal investigator in the German excellence cluster on precision medicine and inflammation. This June, he was first author of the Nature of Use Disease Primers Overview of Atopic Dermatitis. He serves as an associate editor of the Journal of Allergy and Clinical Immunology and the British Journal of Dermatology, and his work has been recognized with the Karl Herxheimer Medal and the Paul Langerhans Prize among others.

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That combination of deep biology, clinical practice and large real world patient data is exactly the perspective we need for today's discussion. Professor Weidinger, thank you for joining us. Gentlemen, the floor is yours and I now hand it off to Jonathan Back, our head of scientific program lead for autoimmunity.

Dr. Jonathan Back – Director, Autoimmunity, and Scientific Program Lead, Egle Therapeutics (03:36):

Thank you, John. Let's take a closer look now at the scientific foundation of the EGL-003 project. Autoimmune and inflammatory diseases can be viewed as a system level imbalance. Inflammatory

effector mechanisms outweigh the regulatory control capacity of the immune system. And while most standard therapies act by suppressing individual inflammatory mediators, our approach is to boost the regulation side of it and enhancing the immune regulation mechanisms really aims at restoring immune homeostasis, which holds a better potential for disease modification and durable control and this without the broad immunosuppression. Now, a key challenge is the disease heterogeneity. Different autoimmune and inflammatory diseases are driven by various combinations of immune pathways that are often active simultaneously. For example, atopic dermatitis is driven mainly by Th2 responses, but can evolve toward Th1 or Th17 polarization as well, which means a single cytokine blockade may be insufficient for durable disease control and other diseases can involve cytotoxic T-cells or the B-cell and autoantibodies axis.

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And because no single downstream effector mechanism controls the full pathology, there is a strong rationale for targeting an upstream regulator that can influence multiple immune nodes simultaneously. IL-2 provides that upstream control point by expanding and activating regulatory T-cells or T-regs, which are, as John previously mentioned, the immune system's natural brake on inflammation and autoimmune responses. And T-reg can regulate multiple effector axis of the immune system, including the different flavors of T-helper responses, but also cytotoxic T-cell responses as well as B-cell and autoantibody responses. Therefore, this upstream mechanism is really intended to restore homeostasis rather than simply quench a single inflammatory output, and that creates the potential for disease modification, durable drug control, and broad applicability across autoimmune and inflammatory diseases. Now on next slide. So what is EGL-003 and how does it manipulate Tregs?

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So natural IL-2 holds one major caveat. It can activate Tregs of course, but can also very efficiently activate effective T cells which are pathogenic in inflammatory and autoimmune diseases as we just saw. And EGL-003 is an FC fused IL-2 mutein designed to selectively agonize Tregs while conserving native IL-2 like potency. So the molecule is designed to spare conventional CD4 and CD8 effector T cells while driving robust Treg expansion, enhance their suppressive function and induce tissue repair and homeostasis for inflammatory and autoimmune diseases. So the remainder of this presentation will highlight, as John mentioned, that in the phase one single ascending dose study, EGL-003 was well tolerated across all tested doses and produced selective long-lasting Treg expansion and granted these cells key effective functions required for effective disease control. But before that, let's quickly look at the engineering underlining EGL-003 activity. So the key structural distinction of EGL-003 is that it combines two complementary type of mutations.

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Selectivity mutations that reduce binding to the IL-2 receptor beta-gamma, that is expressed by effector T cells and NK cells, and potency mutations that stabilize the binding to the alpha beta-gamma receptor that is expressed at high level on Tregs. This really contrasts with earlier generation IL-2 mutants that were designed around selectivity only. And we use here the AMG-592 molecule as a prototypical example. These molecules achieve high selectivity for Tregs, but they lost potency in the process and were incomplete agonists. EGL-003 is designed really to retain wild-type-like agonism on Tregs while maintaining high selectivity, enabling physiological IL-2 signaling in Tregs while minimizing activation of conventional effector cells. We tested how the molecular design of EGL-003 translated into capacity to resolve inflammation, and for that we perform a genetically humanized IL-2 receptor mouse model of intestinal inflammation. In this model, treatment with EGL-003 led to a significant inflammation and disease resolution and clearly outperforming the AMG-592 generation one mutein.

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The ability to resolve inflammation correlated highly with an increase in colonic Tregs and the acquisition of a mucosal healing phenotype by these colonic Tregs. And here again, EGL-003 outperform AMG-592 on these measures, supporting the hypothesis that full Treg agonism may be important to improve the control of inflammation in affected tissues by fully activated Tregs. And I will now hand over to Kenji Hashimoto, our CMO for the clinical part.

Dr. Kenji Hashimoto – Chief Medical Officer, Egle Therapeutics ([10:35](#)):

We will now turn to the phase one single-ascending dosage study and the first clinical data with EGL-003. The SAD study enrolled 24 healthy volunteers across four dose levels ranging from 0.5 to five microgram per kg. Each subject received a single subcutaneous administration of EGL-003 and the study was designed to assess the safety to define the biological effective dose range and to inform dosing frequency for the subsequent clinical studies. The 2.5 microgram per kg cohort was followed through day 56 to provide a longer view of pharmacodynamic and durability. The other cohorts were followed through day 28. This slide summarizes the safety profile and the three was well tolerated across all four cohorts and there was no serious adverse events reported.

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Most common adverse events were injection site reactions and they were all mild and self-limited. Symptoms were limited to the two highest dose cohorts, one mild and one moderate at 2.5 and two mild at 2.5 microgram per kg. Overall, the EGL-003 safety profile supports further development in the upcoming MAD study. Now we move on to the biomarker strategy. In this SAD study, the biomarker strategy was designed to connect exposure to safety, pharmacology and TREG function using both CRAM and immune cell readout. In CRM, we assessed inflammatory cytokines, pharmacokinetics and anti-drug antibodies and IL-10 as a functional suppressive cytokine that is produced by Tregs.

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In immune cells, we assessed IL-2 receptor signaling through pSTAT5. We also used the flow cytometry to evaluate TREG expansion, activation, selectivity and the skin homing potential. Together, these readouts were intended to support dose selection and to establish proof of mechanism that EGL-003 is selectively engaging and activating Treg as designed. In the next few slides, we will focus on the IL-10 and the immune cell characterization, and I would like to give you some highlights here. The integrated biomarker data showed the pattern we hope to see. No inflammatory cytokine elevation, exposure as predicted, and no anti-drug antibody observed in the FAD study.

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We also observed dose-dependent selective pSTAT5 induction in Tregs and selective Treg expansion activation and the skin homing ability. As we expected, EGL-003 produced a dose-dependent amplification of total Tregs across all four dose levels. And importantly, the expansion remained selective. We did not observe corresponding amplification of conventional CD4, CDF T-cells or NK cells. This activity is consistent with the intended molecular design of EGL-003 to expand only the regulatory arm of the immune system. In the long-term observation cohort at 2.5 microgram per kg, the Treg expansion was sustained with elevated total Treg observed through day 28 after a single subcutaneous dosing. The IL-2 kinetics was also associated with the Treg expansion kinetics, and that part arrived in a suppressive IL-10 supports the conclusion that EGL-003 is not simply increasing Treg numbers, but the amplified Treg cells are actually biologically active. We also looked at the phenotype of the expanded Tregs at day eight, and across markers including CD25, CTLA-4, FOXP3, ICOS, HREDR and the Ki-67, we observed the consistent dose-dependent upgradation of markers associated with TREG activation, proliferation, and suppressive function.

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This provides another layer of evidence that EGL-003 is generating activated functional Tregs rather than simply increasing the number of circulating Treg cells. We then examined the CLA, which is a marker of skin forming availability. As you can see, CLA-positive Tregs expanded and subsequently declined below baseline in the blood. This kinetic pattern is consistent with migration out of the circulation and then into tissue, which in this case is the skin for this Treg population.

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Interestingly, in contrast, CLA-negative Tregs remained elevated in the circulation. For an atopic dermatitis program, this is particularly encouraging because it supports the hypothesis that activated Tregs can be generated peripherally and then trafficked towards the skin. Tissue migration will need to be directly evaluated in patients, and this is something we will evaluate during the MAD study. Now, using the same CD25-bright gating strategy that is reported in Rezpeg study, EGL-003 produced approximately eight to 21 fold increases across the SAD dose range. And at the lowest tested dose at 0.5 microgram per kg, EGL-003 produced roughly an eightfold increases of CD25-bright Treg, which actually is in the range of Rezpeg at its maximum clinical dose.

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At five microgram per kg, EGRA three reached approximately 21-fold amplification and these data support the potential for substantially greater T-reg amplification while preserving the selectivity observed across the MAD cohorts. Based on the SAD safety and the pharmacodynamic data, the next step is to obtain the clinical proof of concept in the multiple ascending dose study in atopic dermatitis. The MAD study is double-blind, placebo-controlled, randomized study in adults with moderate to severe atopic dermatitis with a flexible design enrolling approximately 50 to 100 patients. The starting regimen is 1.5 microgram per Q4 week dosing with subsequent cohorts allowing Q4 week or Q2 week dosing and doses up to five microgram per kg based on the emerging data and safety review. The primary endpoint is safety and the secondary endpoints include clinical assessment of AD by EV and BIGA scoring and exploratory endpoints including PD markers both in skin and blood.

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Importantly, the study is designed to obtain clinical proof of concept in atopic dermatitis, which is an indication that is clinically validated for IL-2 agonism. The study is planned to start in September 26th with the first patient dosed anticipated in Q4 26. We expect preliminary efficacy data available in Q2 27 and the full data set would be available for Q4 27.

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Now I am going to hand it over to Professor Stephan Weidinger.

Dr. Stephan Weidinger (18:53):

Thank you, Kenji and others for involving me in this discussion. I think that if you look at this from a clinician's perspective, the key point is that despite all the progress that we have made in atopic dermatitis, there is still quite a lot of room for improvement. We now have several very effective systemic treatments, but not every patient achieves the level or durability of disease control we would like to see. And of course in a chronic disease, efficacy always has to be balanced against tolerability, long-term safety, and also treatment burden. I think this figure illustrates that balance quite well. When we very roughly and indirectly compare efficacy and also consider what we know about safety and tolerability, then I would say dupilumab, which was the game changer in AD has certainly set an important efficacy and safety benchmark. It works very well for many patients and currently it is widely seen as kind of standard of care for moderate to severe AD.

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However, conjunctivitis remains relevant. Some patients have incomplete responses or insufficiently durable control.

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Not all body areas respond equally well or equally quickly. And we also occasionally see less common adverse events or paradoxical inflammatory reactions such as psoriasis or arthritis. Lebrikizumab is a newer alternative for atopic dermatitis with efficacy and safety probably largely comparable to dupilumab. On the other hand, JAK inhibitors can achieve very high and rapid levels of skin clearance and rapid itch improvements in particular at high doses, but systemic safety considerations, warnings and monitoring requirements somewhat limit the attractiveness for some patients. At the same time, the landscape continues to evolve, which is great. We may soon have antibodies with substantially extended half-lives such as zumilokibart, which has shown easy 75 responses in the mid 60% range in phase two, and it's being developed with infrequent maintenance dosing and that could clearly reduce treatment burden. There may also be bi and multi-specific antibodies and antibodies in the future.

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On the other hand, we also have new mechanisms such as Rezpeg, which has demonstrated clinical activity in atopic dermatitis, but so far the efficacy has been more moderate, I would say, than that seen with the leading biologics, while injection site reactions occurred in around 70% of treated patients in phase 2B. So again, efficacy, tolerability and convenience all matter, of course. And this is, I think, where EGL-003 becomes interesting. The single dose study gives us an encouraging first signal on tolerability with predominantly mild adverse events and injection site reactions as the main observation. But what really matters now is that repeated dose study that we have heard about, it has to show that the strong biological signal that selective expansion and activation of Tregs really translates into clinically meaningful and durable benefits while maintaining that favorable safety and tolerability profile. If that combination can be achieved, EGL-003 could offer a really differentiated option in atopic dermatitis.

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And perhaps the simplest way to summarize the rationale is that EGL-003 is not designed simply to suppress one downstream inflammatory effector molecule or pathway. The idea is more to intervene further upstream by selectively activating regulatory T-cells and in that way to help to restore the immune system's own regulatory balance. Conceptually, I think that creates several potential advantages. The ability to influence multiple inflammatory pathways at the same time, the possibility of achieving a more durable control if immune homeostasis can really be restored, and applicability beyond atopic dermatitis, and also the prospect of doing this without broad immunosuppression. The phase one data that we have seen are really encouraging because they support the core pharmacology behind that concept, the selective and sustained Treg expansion, the evidence of functional activation and the favorable initial probability profile, but disease modification and durable treatment control, for example, remain hypothesis at this stage.

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So the next studies now really have to show whether this biological promise in the end translates into meaningful and lasting benefit for patients. So basically, I think the ambition is quite straightforward, reset the immune balance, sustain disease control and reduce treatment burden.

John Celebi, Chief Executive Officer, Egle Therapeutics (24:03):

Professor Weidinger, thank you. That was a genuinely valuable perspective and we're grateful you made the time for us. Thank you also to my colleagues at Egle who presented the data today and to all of you

for spending the time with us. The level of engagement here is a good reminder of how much there is still to work out in atopic dermatitis. Let me leave you with what comes next. Our multi-dose study of EGL-003 in patients with atopic dermatitis is our central focus, and we expect our first efficacy data from that study in mid 2027 with additional dose levels and dosing schedules reading out later in the year. That will be the first look at whether the regulatory T-cell biology we discussed today translates into clinical benefit for patients. Thank you all again. We look forward to sharing what we learn.