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Individualized Cell Therapy Medicine and Manufacturing with an Immunomodulation Platform using T-Regulatory Cells for Program in Type 1 Diabetes Mellitus

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- David J. Mazzo, PhD

CEOCFO: ***Dr. Mazzo, would you tell us what attracted you to Caladrius?***
Dr. Mazzo: There are a number of things that attracted me to Caladrius but principal among them was the interesting pipeline of technologies on the therapeutics side, in combination with growing a very reputable business on the contract development and manufacturing side via our PCT subsidiary. I thought that there were tremendous synergies between those two portions of the business and it was a unique business model. The company had some challenges in terms of managing its therapeutic pipeline. I was looking for a new challenge in a place where I thought there was tremendous potential.

CEOCFO: ***What has been happening over the past year?***
Dr. Mazzo: 2016 has been a pivotal year for Caladrius. We started the year by announcing that we were implementing a new strategic plan. During 2015, we had been executing a Phase III program in immune oncology, but as the environment for melanoma products rapidly changed with the advent and the acceptance of checkpoint inhibitors as a predominant therapy, it became apparent that the program no longer had a competitive edge. We made the difficult (but what we thought was the correct) decision to shelve that program and divert the capital to other interesting technologies. In so doing, we identified and brought forward a program in type 1 diabetes. Our CLBS03 program is a platform for autoimmune disease, which uses a T-regulatory cell approach. We initiated a rigorous Phase II program back in the spring and have been making great progress with that program throughout the year with the completion of the first 18-patient cohort during the summer on schedule. We also recently announced the positive safety assessment from our independent Data Safety Monitoring Board and the initiation of

enrollment in the second cohort of patients for the Phase II trial. That program is moving on, or even slightly ahead of, schedule.

CEOCFO: ***What is the science behind CLBS03?***
Dr. Mazzo: Most autoimmune diseases can be described as being the result of an imbalance between two specific types of cells in the human immune system: the T-regulatory cells (which, as the name implies, help to regulate or control the immune system's attack on foreign bodies), and the T-effector cells (which are the attacking cells that rid the body of foreign pathogens). When you have an autoimmune disease the normal balance of the immune system is lost and normal cells in the body (such as the insulin producing cells of the pancreas) are attacked as if they were foreign invaders. Over time, the effector cells kill the beta cells and reduce and ultimately eliminate your ability to produce insulin, making you totally dependent on an external source of insulin to stay alive. Our approach is to use each patient's own T-regulatory cells, which we collect through a simple blood draw, then to isolate, expand, activate and then return those cells to that same patient. When we do that, we believe we restore the immune balance that should be the natural state between T-regulatory cells and T-effector cells, which should stop disease progression and reduce or eliminate the need for insulin use.

CEOCFO: ***What else is happening at Caladrius?***
Dr. Mazzo: As part of the execution of this study we have actually solidified a relationship with an external research partner called Sanford Research, which is a large research foundation based in the US. Sanford Research has as one of its strategic goals the eradication of type 1 diabetes. Sanford has been providing operational resources of support to the study to help defray costs, but more recently became an investor in Caladrius. In the course of the year we also received Fast Track designation from the US FDA. We believe this is the first type 1 diabetes program that has ever received such a designation, and that is something of which we are very proud.

We also have a platform of technologies that is applicable in cardiovascular disease, specifically in the area of ischemic repair, or fixing tissue that has been damaged by having an insufficient supply of oxygenated blood, such as occurs with a heart attack. This is our CD34 cell therapy platform. During the course of this past year we reached agreement with the Japanese regulatory authorities on a 35-patient, open label, Phase II trial that, if successful, would lead to early conditional approval in Japan, in the indication of critical limb ischemia. In this way, we have advanced our therapies and provided for what is now a development program that is fully defined and ready to execute, without deploying any of our own capital. We will execute that program as soon as we consummate a partnership with a partner in Japan; those discussions are ongoing. Similarly, in that same platform, we see quite a lot of interest in other areas of cardiovascular disease, such as coronary microvascular dysfunction, which is a disease that particularly afflicts women, as well as refractory angina and chronic heart failure. We have grant applications out for all three of those indications to a variety of agencies, and over the course of the next six to nine months we should be hearing about the results. We think there is a very good likelihood that at least one of those trials will be funded fully so that we can move that technology forward in what will likely be considered Phase II programs. Therefore, we have some interesting and creative options to diversify our

pipeline and to exploit this technology that we own, without having to spend much capital on it.

CEOCFO: What about PCT?
Dr. Mazzo: Our subsidiary, cell therapy contract manufacturing partner PCT, has had a wonderful year. We started the year by announcing in March the collaboration with Hitachi Chemical, which formed one of the most interesting global alliances in cell therapy contract development and manufacturing in the industry. Hitachi purchased 19.9% of the PCT subsidiary from Caladrius in return for $19.4 million. That validates what we believe the PCT portion of our business is worth, and that validation now comes from an independent multi-billion-dollar international corporation.

In addition, we agreed to a licensing deal that brought in another $5.6 million, for which we transferred to Hitachi a certain degree of know-how and some processes and systems so that they could establish with our aid a sister company in Yokohama, Japan, called Hitachi PCT. That company will begin operation in April of 2018, and from that, we will derive a milestone of fees and royalties on revenue. It is a great way for PCT to expand into a part of the world where we would not be able to go any time soon, to form a global collaboration with a company that has deep engineering experience to complement our already-advanced engineering experience at PCT. It is also a great way for us to offer to our clients the possibility of moving technologies and products from region to region in a seamless way, which is important for them as they expand their registrations from the US, Japan and beyond. We think this is a great strategic and financial move for us. We brought in $25 million of non-dilutive capital and it set the stage for additional growth and collaborations at PCT.

CEOCFO: *What do you understand about cell therapy manufacturing that others may not?*
Dr. Mazzo: Most cell therapy manufacturing, especially in the early parts of development, involve many unit operations that are manually executed, meaning lots of people doing lots of manual tasks in a clean room environment. It is very labor-intensive and very costly and time consuming. Over time, one needs to be able to reduce many of those manual operations to automated operations in purpose-built equipment in which, ultimately, you could run the entire manufacturing process outside of a classified area—in a typical factory rather than having to run in Class 1,000 or Class 10,000 clean rooms with lots of people being involved. Such automation will ultimately increase efficiency, decrease cost of goods, and remove possibilities of contamination and a number of other issues that one generally deals with when handling highly sensitive materials in these types of environments.

That is something that PCT has really developed a reputation for doing extremely well; not only executing on the actual automation and automation steps, but also being able to counsel clients as to when it is appropriate to do so. If you automate too early in your clinical development, that can be a waste of investment if your product does not advance to the next clinical stage. If you automate too late in development, there will likely need to be extensive comparability testing to convince the regulatory authorities that what you are making is still identical to what was previously made under variations of the similar

process. Knowing when and how to automate is a particular art and something that PCT is quite good at.

CEOCFO: ***Are you expanding your PCT facilities in New Jersey?***
Dr. Mazzo: That's right! We are actually expanding our Allendale, NJ location, building out all of the remaining space to include a couple of additional clean rooms, to qualify some of that space for both European as well as US manufacturing standards so that we can service our European clients out of that facility as well. The expansion will also allow that facility to be a commercial launch facility, effectively offering the capacity and infrastructure to launch a commercial product in the near future. That is very important to us. We have our Mountain View facility in California where we offer similar skills and services to our clients, but there, we have primarily focused that facility on clinical development and manufacturing for the near term.

CEOCFO: ***What is the key as CEO to having many irons in the fire and staying focused?***
Dr. Mazzo: You do it by constantly reminding yourself of some simple rules that most people would find obvious. It is easy, especially if you are as passionate as we all are, to try juggling many projects simultaneously. As a CEO, you are always generating new ideas and you want to pursue them. You always have ways to improve and you want to pursue them. The fact is that you have to recognize the limitations of resources on the human side, because people can only accomplish so much while still doing it well. Additionally, you must recognize that you can only spend the money you have, so I think it is important to be fiscally disciplined, to focus, and to start projects that you can finish. What is more important than having many irons in the fire is being able to pull a few of them out of the fire from time to time and turn them into products. We want to have an appropriate level of sustainability in both the therapeutics pipeline and the PCT business, but we also want to remain sufficiently focused so that we can complete the projects that we are working on and take them to the next available milestones.

CEOCFO: ***Caladrius is a public company; what is the financial picture like today?***
Dr. Mazzo: The financial picture for us is quite good. In many cases, it is an antithesis of what other small-cap biotech companies, especially in the cell therapy space, are facing. We recently completed a $25 million raise that was a combination of private investments in public equity as well as a registered direct offering. We did that at what was then our at-market trading price on the NASDAQ, with no discount and no warrant coverage. In today's environment, that is almost unheard of. Most people are experiencing on average 20%-30% discounts on pricing and warrant coverage that runs from 50%-100% in typical deals. I think that points not only to our ability to find creative ways to acquire the lowest-cost capital available, but also reflects on the potential and promise that these investors (which were a combination of reputable US and international investors) see in our company. We have stabilized through a combination of capital raises, licensing transactions, equity deals such as the Hitachi deal, as well as a number of other projects that are going on, in concert with focusing on fiscal discipline, reducing our burn, and being very efficient. In this way we have been able to stabilize the finances of the company, giving us the opportunity to spend at least as much time on executing our strategy as we have on raising money to support it.

CEOCFO: ***What surprised you as you have been going full-throttle at Caladrius?***

Dr. Mazzo: From the very beginning of when the new leadership team came on board at Caladrius, in early 2015, there were periods of extreme change and challenge. We needed to raise significant money to keep the company afloat. Beyond that, looking at the last 18 months, this newly formed team has been executing impeccably on the strategy that we have announced. We have told people exactly what we are going to do, when we are going to do it and how much it was going to cost, and what they should expect if the results are either positive or negative. To some extent, my biggest surprise (and frustration) is that the general market still has not given us credit for what we have accomplished, for the potential of our company and for the transparency and excitement that we have communicated. I am hoping that this is something that will change for the better in the near future.