June 22, 2022

180 Life Sciences Corp. Issues Letter to Stockholders

PALO ALTO, Calif., June 22, 2022 (GLOBE NEWSWIRE) -- 180 Life Sciences Corp. (NASDAQ: ATNF, “180 Life Sciences” or the "Company"), a clinical-stage biotechnology company today released the following letter to stockholders from its Chief Executive Officer, Dr. James Woody.

Dear Fellow Stockholders,

After our press release press of last week, which included a synopsis of the letters received from the UK Medicine and Healthcare products Regulatory Agency (MHRA) and the US Food and Drug Administration (FDA), we received numerous requests from our stockholders to clarify our plans at 180 Life Sciences for developing a novel therapy for patients with early-stage Dupuytren’s disease and I would like to take this opportunity to bring you up to date.

Our overall aim continues to be to develop new, patented uses for anti-tumor necrosis factor (TNF) therapy for major unmet medical needs. To achieve this, we plan to:

(1) Perform innovative “translational” clinical research to improve medical care for important unmet medical needs; and
(2) Execute on our business objectives to bring beneficial therapies to patients, and thus deliver value for our investors.

Due to the determination, dedication, and expertise of our consultant Prof. Jagdeep Nanchahal, who leads our clinical trials, we have been able to complete the first large-scale trial for early-stage Dupuytren’s disease, which was able to continue due to Prof. Nanchahal’s leadership, unlike many other trials that were closed due to the COVID-19 pandemic. Early-stage Dupuytren’s disease (DD) affects millions of patients in the US and Europe and for which there is currently no approved therapy. Importantly, there are no randomized, placebo-controlled trials to support other possible treatments, including the use of radiotherapy or corticosteroids. Therefore, at present, patients have to wait until their fingers are curled into the palm of the hand before being offered relief via surgery or collagenase, both of which have shortcomings, including the risk of recurrence of the disease.

A problem to overcome when aiming to fulfil unmet needs is the need to design new trials for conditions where there are no previously validated endpoints. Our endpoints for early-stage Dupuytren’s disease, nodule hardness and size, were selected so as to obtain quantitative information in a reasonable timeframe, i.e., 1-2 years, as opposed to a trial that followed patients for a much longer period. For example, a trial using clinical endpoints based on finger contraction or loss of hand function would take about 10 years. We believe that our expert, Prof. Nanchahal, who led our blinded randomized (meaning that patient and medical staff do not know what treatment a patient received) placebo controlled trial, chose

innovative, insightful and practical endpoints based on his deep knowledge of the biology and clinical course of this disease.

Our trial met its primary endpoint, the hardness of the injected nodules and, importantly, also the secondary endpoint of nodule size. These were pre-specified before the clinical trial was started, so there is no 'cherry-picking' of data. The nodule in patients with early-stage Dupuytren's disease is the site where the cells which drive the disease process reside and in our trial the nodule was injected four times over nine months with adalimumab, an inhibitor of TNF, or the placebo, saline. The results were highly statistically significant, and were published in *The Lancet Rheumatology* in April 2022, and subsequently announced. This Phase 2b trial followed on from a prior Phase 2a trial which established the optimal dose of adalimumab to inject into the nodule.

Since statistical significance is not understood by all, allow me to explain that in layman's terms. The conventionally accepted threshold for statistical significance, which means the possibility that the results obtained might be due to random chance, is less than one in 20. This is summarized as a 'p' or probability value of less than 0.05, which is written as $p<0.05$. Only a p value of less than 0.05 is considered significant. Furthermore, the lower the p value, the greater the statistical significance. In our trial for nodule hardness, the statistical significance at 12 months was $p=0.0002$ (which is 250 times less than the accepted minimum, and hence much more significant, meaning there was only 1 chance in 5,000 that this result might have occurred by chance), and for nodule size (area), the statistical significance was $p=0.0025$ (20 times less than the minimum threshold for statistical significance) at 12 months. Importantly, both parameters continued to progressively decrease further for 9 months after the last injection, ($p<0.0001$ for both nodule hardness and nodule size, i.e., 500 times less than the minimal threshold for statistical significance). Thus, we can infer that the local injections of adalimumab were having highly statistically significant and lasting effects.

Next, I would like to discuss the process of interacting with the regulatory agencies in order to gain marketing approval for drugs and biologics, whether they be in the United Kingdom, European Union, or with the FDA here in the US. This process is complex. It is always lengthy and iterative, meaning that questions and responses relating to the requirements for eventual approval go back and forth over many months. Therefore, it may take us the rest of the year or longer to come to an agreement with the UK's MHRA and maybe even longer with the FDA as to what is necessary to gain UK and US marketing authorization. It is always difficult to encapsulate these discussions in a brief press release. Therefore, while we will periodically provide updates as important details become resolved, we will not be commenting on all of our interactions with the regulatory agencies moving forward.

We also believe that there are other points in the MHRA letter that were not emphasized in the press release from last week that we believe are worth mentioning for clarification.

- First, the MHRA did not require us to produce any non-clinical data to support the use of anti-TNF in patients.

- Second, the MHRA agreed that statistical methods used to analyze the data from the trial were appropriate and that the results were highly statistically significant.

- Third, the MHRA noted that the safety profile of adalimumab for early-stage

Dupuytren's disease is likely to be more favorable than the approved indications based on the lower frequency of injections. It is important to note that adalimumab has been used in millions of patients with inflammatory diseases.

- Fourth, the MHRA indicated that they would not require another trial for the use of an adalimumab biosimilar for early-stage Dupuytren's disease.

It is important to note that none of the foregoing represents final definitive positions – the agency reserves the right to come to different determinations in the future.

In response to the questions surrounding our end points, we will be making a case to the MHRA to support our position that nodule size is a relevant 'surrogate marker', meaning a proxy for clinical disease progression, based on existing published data linking nodule size and eventual finger contraction.

While the choice of selecting relevant endpoints for the Dupuytren's trial is complicated because the disease progresses slowly and no such trial had ever been done before, the future trials in frozen shoulder and post-operative delirium that the Company plans to conduct do not face the same challenges, because these disorders develop over much shorter time scales. The planned trials in patients with frozen shoulder and post-operative delirium will assess the feasibility of conducting phase 3 clinical trials with what we believe will be validated registration endpoints acceptable to the regulatory agencies. As always, whether and when the Company conducts any such additional trials will depend on regulatory authorizations, resources, including available funding and various other factors.

It is worth noting that for Dupuytren's disease and frozen shoulder, Prof. Nanchahal and the team working with him have been awarded peer reviewed grants from public agencies to support a significant part of the costs of these trials. We believe this is noteworthy as this testifies to the perceived quality and competitiveness of the work, which provides non-dilutive funding, as only a very small percentage of proposals are funded.

To summarize, 180 Life Sciences continues to progress with its innovative clinical development program. We are working diligently and efficiently in order to deliver our aims for the benefit of patients and our investor community. We look forward to providing you future updates as our development program continues to mature.

I also want to thank you, our stockholders, for your continued support of 180 Life Sciences Corp.

Sincerely,

James Woody MD, PhD

CEO, 180 Life Sciences

About 180 Life Sciences Corp.

180 Life Sciences Corp. is a clinical-stage biotechnology company. The Company is driving groundbreaking studies into clinical programs, which are seeking to develop treatments for major unmet clinical needs. The Company's primary platform is a novel program to treat inflammatory disorders using anti-TNF (tumor necrosis factor).

Forward-Looking Statements

This press release includes “forward-looking statements”, including information about management’s view of the Company’s future expectations, plans and prospects, within the safe harbor provisions provided under federal securities laws, including under The Private Securities Litigation Reform Act of 1995 (the “Act”). Words such as “expect,” “estimate,” “project,” “budget,” “forecast,” “anticipate,” “intend,” “plan,” “may,” “will,” “could,” “should,” “believes,” “predicts,” “potential,” “continue” and similar expressions are intended to identify such forward-looking statements. These forward-looking statements involve significant risks and uncertainties that could cause the actual results to differ materially from the expected results and, consequently, you should not rely on these forward-looking statements as predictions of future events. These forward-looking statements and factors that may cause such differences include, without limitation, statements about the ability of our clinical trials to demonstrate safety and efficacy of our product candidates, and other positive results; the uncertainties associated with the clinical development and regulatory approval of 180 Life Science’s drug candidates, including potential delays in the enrollment and completion of clinical trials, issues raised by the FDA and MHRA, timing to complete required studies and trials, and timing to obtain governmental approvals; the potential that earlier clinical trials and studies may not be predictive of future results; 180 Life Sciences’ reliance on third parties to conduct its clinical trials, enroll patients, and manufacture its preclinical and clinical drug supplies; the ability to come to mutually agreeable terms with such third parties and partners, and the terms of such agreements; estimates of patient populations for 180 Life Sciences planned products; unexpected adverse side effects or inadequate therapeutic efficacy of drug candidates that could limit approval and/or commercialization, or that could result in recalls or product liability claims; 180 Life Sciences’ ability to fully comply with numerous federal, state and local laws and regulatory requirements, as well as rules and regulations outside the United States, that apply to its product development activities; the timing of filing, the timing of governmental review, and outcome of, planned Investigational New Drug (IND) applications for drug candidates; current negative operating cash flows and a need for additional funding to finance our operating plans; the terms of any further financing, which may be highly dilutive and may include onerous terms; statements relating to expectations regarding future agreements relating to the supply of materials and license and commercialization of products; the availability and cost of materials required for trials; the risk that initial drug results will not be able to be replicated in clinical trials or that such drugs selected for clinical development will not be successful; challenges and uncertainties inherent in product research and development, including the uncertainty of clinical success and of obtaining regulatory approvals; uncertainty of commercial success; the inherent risks in early stage drug development including demonstrating efficacy; development time/cost and the regulatory approval process; the progress of our clinical trials; our ability to find and enter into agreements with potential partners; our ability to attract and retain key personnel; changing market and economic conditions; our ability to produce acceptable batches of future products in sufficient quantities; unexpected manufacturing defects; manufacturing difficulties and delays; competition, including technological advances, new products and patents attained by competitors; challenges to patents; product efficacy or safety concerns resulting in product recalls or regulatory action; changes in behavior and spending patterns of purchasers of health care products and services; changes to applicable laws and regulations, including global health care reforms; expectations with respect to future performance, growth and anticipated acquisitions; the continued listing of the Company on The NASDAQ Stock Market; expectations regarding the capitalization, resources and

ownership structure of the Company; expectations with respect to future performance, growth and anticipated acquisitions; the ability of the Company to execute its plans to develop and market new drug products and the timing and costs of these development programs; estimates of the size of the markets for its potential drug products; the outcome of current litigation involving the Company; potential future litigation involving the Company or the validity or enforceability of the intellectual property of the Company; global economic conditions; geopolitical events and regulatory changes; the expectations, development plans and anticipated timelines for the Company's drug candidates, pipeline and programs, including collaborations with third parties; access to additional financing, and the potential lack of such financing; and the Company's ability to raise funding in the future and the terms of such funding. These risk factors and others are included from time to time in documents the Company files with the Securities and Exchange Commission, including, but not limited to, its Form 10-Ks, Form 10-Qs and Form 8-Ks, and including the Annual Report on Form 10-K for the year ended December 31, 2021 and Quarterly Report on Form 10-Q for the quarter ended March 31, 2022, and future SEC filings. These reports and filings are available at www.sec.gov and are available for download, free of charge, soon after such reports are filed with or furnished to the SEC, on the "Investors"—"SEC Filings"—"All SEC Filings" page of our website at www.180lifesciences.com. All subsequent written and oral forward-looking statements concerning the Company, the results of the Company's clinical trial results and studies or other matters and attributable to the Company or any person acting on its behalf are expressly qualified in their entirety by the cautionary statements above. Readers are cautioned not to place undue reliance upon any forward-looking statements, which speak only as of the date made, including the forward-looking statements included in this press release, which are made only as of the date hereof. The Company cannot guarantee future results, levels of activity, performance or achievements. Accordingly, you should not place undue reliance on these forward-looking statements. The Company does not undertake or accept any obligation or undertaking to release publicly any updates or revisions to any forward-looking statement to reflect any change in its expectations or any change in events, conditions or circumstances on which any such statement is based, except as otherwise provided by law.

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