September 26, 2022

180 Life Sciences Issues Letter to Stockholders

PALO ALTO, Calif., Sept. 26, 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 Stockholder,

In mid-June, I wrote to update you on the status of our Company and our respective investments.

In that letter, I provided an update regarding the Company's clinical development plans, which remained on track then, and continue to remain on track today. As a reminder, 180 Life Sciences was founded on the belief that novel anti-inflammatory biologics that are already approved, such as anti-tumor necrosis factor (TNF), or adalimumab, could have the potential to address large unmet needs for a variety of additional indications. Currently, we have an active clinical development program that includes Phase 2a and Phase 2b proof-of-concept data which we believe demonstrates that anti-TNF therapy can prevent the progression of Dupuytren's disease in its early stages, as well as plans for two additional Phase 2 studies, one in frozen shoulder which has recently commenced, and the other in post-operative cognitive delirium (POCD), for which we just received grant funding. The POCD grant will allow 180LS to determine if administration of an anti TNF antibody, just prior to surgery, either reduces or eliminates the cognitive delirium often seen following surgery. This will be a randomized controlled clinical trial using Remsima, an anti TNF antibody supplied by Celltrion. We think all three indications share a similar underlying mechanism of being critically dependent on TNF. (1-3).

Fibrosis of the hand, known as Dupuytren's disease, is a common chronic, progressive condition that causes the fingers to curl irreversibly into the palm and can be very disabling. In the early stage of the disease, TNF and other pro-inflammatory cytokines, recruit myofibroblasts that lead to fibrosis and the formation of a tiny lump, or nodule, in the palm of the hand. The nodule is the site where the cells which drive the disease reside. Approximately 20-35% of patients with a palmar nodule progress to finger contractures. (4). Patients with comorbidities, such as smoking and diabetes, are more likely to experience disease progression. Roughly 12 million patients in the U.S., 2.5 million in the U.K. and 22 million in the EU have Dupuytren's disease.(5). Currently, there is no approved treatment for early-stage disease and patients must wait until the disease progresses with loss of hand function before undergoing surgery or treatment with collagenase. More than 50% of patients will experience a recurrence of Dupuytren's disease within five years of non surgical intervention (6) and about 6 % after surgery (7). As such, there is a very large unmet need for patients with early-stage Dupuytren's disease.

In April, we announced that positive Phase 2b data from our trial in Dupuytren's disease had been published in *The Lancet Rheumatology*. As discussed in that publication, through extensive research of published medical literature, as well as direct clinical and drug development experience, Dr. Nanchahal, Chairman of the 180LS Clinical Advisory Board , believes that the treatment for Dupuytren's disease is most effective during the early nodular stage of the disease, to prevent the development of cords and progression to finger contractures. Dr. Nanchahal's investigation of anti-TNF therapy in Dupuytren's disease in a small Phase 2a study(8) found, that intranodular injection of 40 milligrams (mg) of adalimumab in 0.4 milliliter (ml) resulted in down-regulation of the myofibroblasts that are responsible for fibrosis and the formation of the nodule in the early stage of Dupuytren's disease.

Based upon the Phase 2a findings, he determined that a rigorous randomized, double-blind, placebo-control Phase 2b was warranted in order to attempt to further demonstrate that repurposing anti-TNF therapy for Dupuytren's disease could be an effective treatment for early-stage disease and prevent progression. Based upon published medical literature, clinical experience and the findings from our Phase 2a study, we believed that a primary endpoint of nodule hardness and a secondary endpoint of nodule size could be effective indicators, or surrogates, of long-term disease progression in the absence of a clinical trial with a 10-year follow-up. The trial met its primary endpoint of nodule hardness and, importantly, also the secondary endpoint of nodule size. These were specified before the clinical trial was performed. The results were statistically significant when compared to placebo. Further there is published information indicating that module size correlates with eventual finger contraction (9). The significant and persistent reduction in nodule size as seen in the 2B trial (1) would be expected to delay or eliminate the progression to finger contraction.

This brings us to where we are today. We have a scheduled meeting during Q4 2022 with the U.K.'s Medicines and Healthcare products Regulatory Agency (MHRA) regarding our Phase 2b data in Dupuytren's disease, based on the initial determination by MHRA that our chosen endpoints need further validation. At this meeting, we plan to submit evidence to the MHRA that supports our chosen endpoints. Once this data is submitted, we expect further discussions with the MHRA, in which they are expected to provide final guidance regarding the regulatory approval pathway of an anti-TNF therapy in early-stage Dupuytren's disease. Knowing that this could take several months, we expect to gain clarity from the MHRA by late first quarter of 2023.

We also continue to remain in discussions with potential partners, and/or licensees for our Dupuytren's program.

In terms of additional progress, we recently disclosed that the first patient in the preventative frozen shoulder trial, also funded by a National Institute for Health and Care Research (NIHR) grant, had received an injection in the trial. There are five active sites, and we will be observing how quickly patients can be enrolled in this trial to gain information on the potential use of anti-TNF agents to reduce or eliminate the need for surgical intervention in this debilitating disease. For the POCD trial, we are gathering all the regulatory approvals necessary to initiate patient treatment, anticipated by Q1 2023, or earlier.

In terms of the further development of intellectual property, we continue to make novel discoveries and file new patents. Most recently we discovered another pro fibrotic

mechanistic pathway and showed that by blocking the protein interleukin-33 (IL-33) and TNF receptor 2 (TNF R2), the expression of the pro-fibrotic genes in myofibroblasts could be inhibited. The patent was issued earlier this year.

In closing, we continue to work diligently and efficiently to deliver treatment options for one of the largest drivers of disease, inflammation. Our active clinical development program currently consists of three potential indications and our clinical development plans for all ongoing programs remain on track. We believe that the successful execution of our current clinical development plans over the long-term could enhance stockholder value.

Sincerely,

/s/ James Woody MD, PhD

CEO, 180 Life Sciences

About 180 Life Sciences Corp.

180 Life Sciences Corp. is a clinical-stage biotechnology company driving ground-breaking studies into clinical programs which are seeking to address major unmet medical needs. The Company's primary platform is a novel program to treat several 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 U.S. Food and Drug Administration (FDA) and MHRA; the timing and outcome of the Company's planned meeting with MHRA, including the Company's ability to persuade MHRA that such chosen endpoints do not require further validation; timing to complete required studies and trials, and timing to obtain governmental approvals; 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, increases in interest rates which may make borrowing more expensive and increased inflation which may negatively affect costs, expenses and returns; 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 are not predictive of future results or 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's securities 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; and the effect of economic downturns and recessions. 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 June 30, 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.

Investors:
Jason Assad
Director of IR
180 Life Sciences Corp
(678) 570-6791
Jason@180lifesciences.com

Suzanne Messere
Stern Investor Relations, Inc.
(212) 698-8801
Suzanne.Messere@sternir.com

References:
1. Anti-tumor necrosis factor therapy for early-stage Dupuytren's disease (RIDD): a phase 2b, randomized, double-blind, placebo-controlled trial. Jagdeep Nanchahal, Catherine Ball, Ines Rombach, Lynn Williams, Nicola Kenealy, Helen Dakin, Heather O'Connor, Dominique Davidson, Paul Werker, Susan J Dutton, Marc Feldmann, Sarah E Lamb. Lancet Rheumatology Vol 4 June 2022
2. Smith SP, Devaraj VS, Bunker TD. The association between frozen shoulder and Dupuytren's disease. Journal of Shoulder and Elbow Surgery. 2001;10(2):149-51.
3. Tumor necrosis factor-α triggers a cytokine cascade yielding postoperative cognitive decline; Niccolò Terrandoa, Claudia Monacoc, Daqing Mab, Brian M. J. Foxwellc, Marc Feldmann, and Mervyn Mazea, PNAS 107, 2010 pg;20519
4. Reilly RM, Stern PJ, Goldfarb CA: A retrospective review of the management of Dupuytren's nodules. J Hand Surg Am. 2005; 30(5): 1014–8.
5. The worldwide prevalence of the Dupuytren disease: a comprehensive systematic review and meta-analysis. Nader Salari1, Mohammad Bagher Heydari, Masoud Hassanabadi, Mohsen Kazeminia, Nikzad Farshchian, Mehrdad Niaparast, Yousef Solaymaninasab, Masoud Mohammadi , Shamarina Shohaimi and Alireza Daneshkhah . Journal of Orthopedic Surgery and Research (2020) 15:495
6. Van Rijssen AL, ter Linden H, Werker PM. Five-year results of a randomized clinical trial on treatment in Dupuytren's disease: percutaneous needle fasciotomy versus limited fasciectomy. Plastic & Reconstructive Surg 2012; 129:469–77.
7.Rodrigues JN, Zhang W, Scammell BE, et al.: Functional outcome and complications following surgery for Dupuytren's disease: a multi-center cross-sectional study. J Hand Surg Eur Vol. 2017; 42(1): 7–17.
8. Anti-Tumor Necrosis Factor Therapy for Dupuytren's Disease: A Rand McCann, Marisa Cabrita, Jennifer Swettenhama, Neil J. Cahoonb, Bethan Copsey c, E. Anne Francis Peter C. Taylor a, Joanna Black c, Vicki S. Barber c, Susan Dutton c, Marc Feldmann, Sarah E. Lamb E-Biomedicine 33 (2018) 282–288

9. Clusters in Short-term Disease Course in Dupuytren's Participants With Primary Dupuytren Disease Rosanne Lanting, MD, PhD, Edwin R. van den Heuvel, PhD, Paul M. N. Werker, MD, PhD J of Hand Surgery Am Vol 41: 2016

Source: 180 Life Sciences Corp.