Endo Announces Positive Results from Phase 3 Studies of Collagenase Clostridium Histolyticum (CCH) in Patients with Cellulite

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Both RELEASE-1 and RELEASE-2 Studies Demonstrated Highly Statistically Significant Results (P=0.006 and P=0.002 respectively) on Efficacy Endpoints

DUBLIN, Nov. 7, 2018 /PRNewswire/ -- Endo International plc (NASDAQ: ENDP) announced positive results today from two identical Phase 3 RELEASE* studies of collagenase clostridium histolyticum (CCH) for the treatment of cellulite in the buttocks. Subjects receiving CCH showed highly statistically significant levels of improvement in the appearance of cellulite with treatment, as measured by the trial's primary endpoint (RELEASE-1, p=0.006 & RELEASE-2, p=0.002), which was at least a 2-level composite improvement in cellulite severity in the target buttock at Day 71 as compared to subjects receiving placebo. In addition, RELEASE-1 passed 8 out of 8 key secondary endpoints and RELEASE-2 passed 7 out of 8 key secondary endpoints. CCH was well-tolerated in the actively-treated subjects with most adverse events (AEs) being mild to moderate in severity and primarily limited to the local injection area.

"Based on our review of the Phase 3 data, we remain confident in our CCH program for cellulite—a condition that makes many women self-conscious and prompts them to seek treatment options," said Matthew Davis, M.D., R.Ph., Endo's Senior Vice President and Chief Medical Officer. "If approved, CCH has the potential to be an important new treatment for cellulite and we are excited to take the next steps in that process."

About RELEASE-1 and RELEASE-2
RELEASE-1 and RELEASE-2 are two identical, multicenter, randomized, double-blind, placebo-controlled studies that enrolled 845 women (423 and 422 in each separate trial) aged 18 years or older in the United States with moderate to severe cellulite. Each subject received up to three treatments of CCH (0.84 mg / treatment area) or placebo with each treatment session occurring approximately 21 days apart. Up to twelve injections were administered during each session across each treatment area – the left and right buttock. At both the outset and conclusion of each treatment, cellulite severity was assessed by each patient and clinician using two validated photonumeric cellulite severity scales developed by Endo and third-party psychometric experts.

The primary endpoint of the Phase 3 studies was a composite responder analysis demonstrating at least a 2-level composite improvement independently reported by both patient and clinician on the photonumeric scales of cellulite severity in the target buttock. Key secondary endpoints in target buttocks included the percentage of subjects that experience at least a 1-level or 2-level improvement in patient reported assessment percentage of subjects with a 1-level composite improvement, the percentage of subjects with at least a 1-level or 2-level improvement in the global aesthetic improvement scale (GAIS), as well as percentage of subjects with a 2-level composite improvement in non-target buttocks and also percentage of satisfied subjects, change from baseline in a cellulite impact scale (i.e., patients' self-perception related to their cellulite).

"The Phase 3 results are positive for patients and consistent with previous data that demonstrate CCH has the potential to be a breakthrough treatment for cellulite, a condition that millions of women experience but for which there are currently limited effective treatment options," said Joely Kaufman-Janette, M.D., a board certified dermatologist at Skin Associates of South Florida, and a CCH clinical trial investigator. "Many of my patients have expressed that they are self-conscious about their cellulite and looking for something to effectively treat it. The fact that CCH is a potential new injectable option to treat cellulite will be very meaningful for my patients and for the aesthetics industry overall."

Primary Endpoint for RELEASE-1:

- 7.6 percent of subjects receiving CCH demonstrated a highly significant (p=0.006) improvement in the composite investigators' and patients' assessments of the appearance of cellulite, as measured by a two-level response in both the Clinician Reported- Photonumeric Cellulite Severity Scale (CR-PCSS) and Patient Reported- Photonumeric Cellulite Severity Scale (PR-PCSS) scores, for the target buttock at Day 71, compared to only 1.9 percent of placebo subjects.

Primary Endpoint for RELEASE-2:

- 5.6 percent of subjects receiving CCH demonstrated a highly significant (0.002) improvement in the composite investigators' and patients' assessments of the appearance of cellulite, as measured by a two-level response in both the CR-PCSS and PR-PCSS scores, for the target buttock at Day 71, compared to only 0.5 percent of placebo subjects.

Key Secondary Endpoints for both RELEASE-1 and RELEASE-2:

- 37.1 percent of subjects in RELEASE-1, and 41.6 percent of subjects in RELEASE-2 receiving CCH demonstrated a highly significant 1-level response in the composite investigators' and patients' assessments of the appearance of cellulite, as measured by both the CR-PCSS and PR-PCSS scores, for the target buttock at Day 71, compared to only 17.8 percent and 11.2 percent of placebo subjects respectively.
- 24.3 percent of subjects in RELEASE-1, and 21.0 percent of subjects in RELEASE-2 receiving CCH demonstrated a highly statistically significant 2-level improvement on the patients' assessment of the appearance of cellulite in the target buttock at Day 71, as measured by the PR-PCSS scores compared to only 12.2 percent and 5.8 percent of placebo subjects respectively.
- 54.3 percent of subjects in RELEASE-1, and 57.9 percent of subjects in RELEASE-2 receiving CCH demonstrated a highly statistically significant 1-level improvement on the patients' assessment of the appearance of cellulite in the target buttock at Day 71, as measured by the PR-PCSS scores compared to only 36.2 percent and 29.6 percent of placebo subjects respectively.
- 48.6 percent of subjects in RELEASE-1, and 42.1 percent of subjects in RELEASE-2 receiving CCH demonstrated a highly statistically significant 1-level improvement on the patients' assessment of the appearance of cellulite in the target buttock at Day 71, as measured by the SSRS (Subject Self Rating Scale) compared to only 22.5 percent and 15.0 percent of placebo subjects respectively.
- 54.3 percent of subjects in RELEASE-1, and 46.8 percent of subjects in RELEASE-2 receiving CCH reported being "Satisfied" or "Very Satisfied" with their cellulite treatment as assessed by the Subject Satisfaction with Cellulite Treatment Assessment at Day 71, compared to only 25.8 percent and 13.6 percent of placebo subjects respectively.
- 73.3 percent of subjects in RELEASE-1, and 67.8 percent of subjects in RELEASE-2 receiving CCH were reported as "Improved" or "Very Improved" or "Very Much Improved" in global appearance of their cellulite area as assessed by the Subject- Global Aesthetic Improvement Scale in the target buttock at Day 71, compared to only 43.2 percent and 24.1 percent of placebo subjects respectively.
- Subjects receiving CCH demonstrated a statistically significant improvement in the composite investigators' and patients' assessments of the appearance of cellulite, as measured by a 2-level improvement in both the CR-PCSS and PR-PCSS scores, for the non-target buttock at Day 71 for RELEASE-1 study but failed to show statistical significance in RELEASE-2 study.

Consistent with earlier studies of CCH for the treatment of cellulite, CCH was well-tolerated in the Phase 3 studies by all dose groups with most adverse events (AEs) being mild to moderate and primarily limited to the local injection area. The most common AEs in the trial were injection site bruising, injection site pain, injection site discoloration, injection site nodule and injection site pruritus.

About Cellulite
Cellulite is a localized metabolic disorder of tissue under the skin that has been reported in 85 to 98 percent of post-pubertal females and affects women of all races and ethnicities[i][ii]. The condition can involve the loss of elasticity or shrinking of collagen cords, called "septae," that attach the skin to the muscle layers below. When fat in cellulite prone areas swells and expands, the septae tether the skin, which causes the surface dimpling characteristic of cellulite[iii]. CCH is intended to target and lyse, or break, those collagen tethers with the goal of releasing the skin dimpling and potentially resulting in smoothing of the skin. Despite multiple therapeutic approaches for the attempted treatment of cellulite, there are no

FDA-approved pharmacological treatments and little scientific evidence that any current treatments are beneficial[iv].

About Endo International plc
Endo International plc (NASDAQ: ENDP) is a highly focused generics and specialty branded pharmaceutical company delivering quality medicines to patients in need through excellence in development, manufacturing and commercialization. Endo has global headquarters in Dublin, Ireland, and U.S. headquarters in Malvern, PA. Learn more at www.endo.com.

Forward Looking Statements
This press release contains certain forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995 and Canadian securities legislation, including, but not limited to, the statement by Drs. Davis and Kaufman-Janette, and other statements regarding research and development outcomes, efficacy, adverse reactions, market and product potential and product availability. Statements including words such as "believes," "expects," "anticipates," "intends," "estimates," "plan," "will," "may," "look forward," "intend," "guidance," "future" or similar expressions are forward-looking statements. Because these statements reflect Endo's current views, expectations and beliefs concerning future events, they involve risks and uncertainties. Although Endo believes that these forward-looking statements and information are based upon reasonable assumptions and expectations, readers should not place undue reliance on them, or any other forward-looking statements or information in this news release. Investors should note that many factors, as more fully described in the documents filed by Endo with the Securities and Exchange Commission and with securities regulators in Canada on the System for Electronic Document Analysis and Retrieval, including under the caption "Risk Factors" in Endo's Form 10-K, Form 10-Q and Form 8-K filings, and as otherwise enumerated herein or therein, could affect Endo's future results and could cause Endo's actual results to differ materially from those expressed in forward-looking statements contained in this communication. The forward-looking statements in this press release are qualified by these risk factors. Endo assumes no obligation to publicly update any forward-looking statements, whether as a result of new information, future developments or otherwise, except as may be required under applicable securities laws.

*__R__andomized __E__va__L__uation of C__E__llulite Reduction by Coll__A__gena__SE__ Clostridium Histolyticum (RELEASE)

[i] Avram, Cellulite: a review of its physiology and treatment, *Journal of Cosmetic Laser Therapy* 2004; 6: 181–185.
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[iv] Wanner M et al. An evidence-based assessment of treatments for cellulite. *J Drugs Dermatol*. 2008 Apr;7(4):341-5.

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