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Completion of Investigator-initiated Clinical Trial for the Treatment of Male Stress Urinary Incontinence with Uncultured Autologous Adipose Derived Regenerative Cells in Japan

ADRESU※1, an investigator-initiated clinical trial led by Nagoya University Hospital for the treatment of male stress urinary incontinence using uncultured autologous adipose derived regenerative cells (ADRCs)※2 began enrollment in September 2015. The trial commenced following consultation with the Pharmaceuticals and Medical Devices Agency (PMDA) and successful submission of the Clinical Trial Notification to the Ministry of Health, Labour and Welfare (MHLW) in Japan, in collaboration with Cytori Therapeutics, K.K.

ADRESU is the world's first clinical trial for regenerative medicine-based treatment of male stress urinary incontinence with ADRCs. Nagoya University Hospital conducted the prospective, multicenter, single-arm study (with Dr. Momokazu Gotoh, Professor of the Department of Urology as Coordinating Investigator), in cooperation with Kanazawa University Hospital, Shinshu University Hospital and Dokkyo Medical School Hospital, and supported by the Department of Advanced Medicine at Nagoya University Hospital. ADRCs, prepared with Cytori's Celution® System※3 (consisting of the Celution® Centrifuge and Celution® Cell Therapy Kit) were administered to male patients with stress urinary incontinence and evaluated for 52 weeks to investigate the treatment's efficacy and safety.

ADRESU was completed in March 2019, and a clinical study report has been issued. Male patients with mild to moderate stress urinary incontinence persisting for more than one year and resistant to pharmacological and behavioral therapies were administered a single transurethral endoscopic injection of ADRCs into the periurethral region. Results confirm safety and the primary efficacy endpoint for the trial was achieved.

Based on the successful results of ADRESU, Cytori Therapeutics, K.K., in cooperation with Nagoya University Hospital, is in preparations to apply for medical device marketing approval for the Celution® System, and intends to seek reimbursement coverage under Japan's National Health Insurance System next year (2020).

With the support of The Japanese Urological Association and The Japanese Continence Society, we strive towards improving the quality of life of male patients with stress urinary incontinence as well as developing a regenerative medicine-based treatment using ADRCs.

※1 ADRESU
The subjects of the clinical trial were men with stress urinary incontinence that persisted for more than one year after prostatectomy for prostate cancer or benign prostatic hyperplasia, and resistant to pharmacological and behavioral therapies. Safety and efficacy were evaluated over a 52-week follow-up period after periurethral injection of autologous ADRCs prepared using the Celution® System.

ADRESU was supported by grants-in-aid - the Health and Labour Sciences Research Grant from the Ministry of Health, Labour and Welfare, grants from the Japan Agency for Medical Research and Development, as well as a support grant for advanced research from Nagoya University Hospital.

For more details, please refer to: BMC Urol. 17(1): 89, 2017 （UMIN.ID：UMIN000017901, ClinicalTrials.gov Identifier：NCT02529865）

※2 Regenerative medicine-based treatment of male stress urinary incontinence using ADRCs
About 250 mL of subcutaneous fat was harvested from the abdomen by liposuction under anesthesia, and processed using the Celution® System (provided by Cytori Therapeutics, K.K.) to produce autologous uncultured ADRCs. The ADRCs were transurethrally injected under endoscopic vision into the urethral sphincter, and a mixture of ADRCs and fat tissue was injected into the submucosal space of the sphincter. This novel regenerative medicine-based treatment for stress urinary incontinence caused by urethral sphincter deficiency is safe and minimally invasive, and may be performed within 3 hours in a single procedure without the need for *ex vivo* cell culture.
For more details, please visit:
https://www.med.nagoya-u.ac.jp/uro08/advanced/regenerative-therapy/index.html.

※3 The Celution® System
The Celution® System is a proprietary medical technology platform developed by Cytori Therapeutics to prepare autologous ADRCs for same-day treatment without the need for *ex vivo* cell culture. Physicians and scientists have demonstrated the frequency of stem cells in fat tissue to be 2,500 times greater than the frequency of similar cells in bone marrow[1-3]. Further, fat tissue can be more easily collected than bone marrow, with less co-morbidities[4]. As Cytori technology is based on autologous tissue sources, treatment with ADRCs avoid common transplantation issues such as cell rejection or disease transmission, and does not require anti-rejection or immunosuppressant drugs. The Celution® System is a fully-automated, functionally closed system designed to extract and concentrate regenerative and stem cells found in fat tissue. Freshly isolated (uncultured) ADRCs may be administered in real-time without further

manipulation, retaining pre-existing cell properties and therapeutic benefits.

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