Mallinckrodt Announces Publication of Real-World Data on the Use of Extracorporeal Photopheresis (ECP) in Heart Transplant Patients

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- Results from the largest European and first multicenter, retrospective, observational chart review study investigating the real-world use of ECP in heart transplant patients reinforce its use as a treatment for heart transplant rejection and prevention of rejection[1] -

DUBLIN, June 13, 2023 /PRNewswire/ -- Mallinckrodt plc (NYSE American: MNK), a global specialty pharmaceutical company, today announced the publication of findings from a retrospective, observational, single arm, European chart review study assessing the real-world use of extracorporeal photopheresis (ECP) and its impact on clinical outcomes in the modern era of heart transplantation.[1] An online version of the data manuscript – the largest-known study of ECP in heart transplant patients – is currently published on the *Journal of Heart and Lung Transplantation* website in advance of print publication in the second half of 2023.

Interim results of this study were presented in a late-breaking session at the 20th Congress of the European Society for Organ Transplantation (ESOT) in 2021 in Milan, Italy.[2]

The study, titled "European Multicenter Study on The Real-World Use and Clinical Impact of Extracorporeal Photopheresis After Heart Transplantation," examined data from the medical charts of 105 patients who received ECP following heart transplantation at seven medical centers in Austria, Germany, France, Hungary, and Italy between 2015 – 2021. At time of data extraction, 58 patients (55.2%) had completed their ECP treatment and 47 patients' (44.8%) ECP treatment was ongoing.[1]

"These findings from the largest European and first multicenter study investigating the real-world use of ECP in heart transplant patients support ECP as a treatment for various types of graft rejection and in prevention of graft rejection with varied treatment schedules,[1]" said **Markus Barten, M.D., Surgical Director of Heart Failure Clinic, University Heart and Vascular Center Hamburg**. "This data not only builds upon the growing body of real-world evidence supporting the use of ECP in heart transplant patients, but also reflects the importance of supporting clinicians with treatment modalities for transplant rejection and stabilization.[1]"

About the Study[1]

Mean age of patients at start of ECP was 47.7 (SD 14.4) years (min. 16 years to max. 74 years), and most patients (70.5%) were male. They were followed for a mean time of 25.1 (SD 16.8) months from ECP treatment initiation to last visit at the transplant center (follow-up time for outcome overall survival). Mean time from ECP treatment initiation to last visit right censored at 2 years after the end of ECP treatment was 22.5 (SD 13.7) months (follow-up time for outcomes graft function, response, and complications).

Cardiomyopathy was the primary reason for heart transplantation (n=81 patients; 77.1%), followed by coronary heart disease (n=11 patients; 10.5%), heart valve disease (n=5 patients; 4.8%), and myocarditis (n=5 patients; 4.8%). The main reason to start ECP treatment was acute cellular rejection (ACR; n=37 patients; 35.2%), followed by prevention of rejection (n=34 patients; 32.4%), mixed rejection (n=19 patients; 18.1%), and antibody-mediated rejection (AMR; n=15 patients; 14.3%).

The prevention of rejection subgroup included patients who started ECP treatment without biopsy-proven rejection and with standard or reduced immunosuppressive therapy.

Key Findings[1]

- Graft function was stable for almost all patients throughout the study who completed ECP and had graft function change assessed (97.2%; n=35/36).
- In patients who started ECP to treat ACR, AMR or mixed rejection (n=26), completed ECP treatment and had a biopsy at the start and end of treatment, 92.3% (n=24) were classified as responders, having demonstrated an improvement of ACR and/or AMR International Society for Heart and Lung Transplantation (ISHLT) grading after a mean ECP treatment duration of 5.4 months. The remaining patients had stable grades.
- In patients who started ECP to prevent rejection (n=34), 88.2% (n=30) remained free from any rejection over a mean follow-up of 26 months despite being considered at high risk for rejection and reduced immunosuppressive therapy.
- All patients started ECP treatment while on immunosuppressive therapy, and almost all remained on immunosuppressants until last reported visit prior to data extraction. Tacrolimus and mycophenolate derivatives were the most frequently used immunosuppressants. The number of patients on steroid therapy decreased slightly over time.
- Among patients with ongoing ECP treatment who remained on steroid therapy (n=34), steroid dose was reduced on average by 63.0% from start of ECP to last reported visit for 41.2% (n=14) of patients. Steroid dose increased for 5.9% (n=2) of patients and was stable in 52.9% (n=18) of patients.
- Among patients who completed ECP treatment and remained on steroid therapy (n=42), steroid dose was reduced on

average by 67.0% from start of ECP to last reported visit for 52.4% (n=22) of patients. Steroid dose increased for 4.8% (n=2) of patients and was stable in 42.9% (n=18) of patients.

- Amongst the 19 patients in the prevention group, 16 (84.2%) received tacrolimus at the start of ECP and last reported visit. In 11/16 patients, tacrolimus trough levels were available of which 7 (63.6%) patients experienced an average trough level decrease of 34.0%.
- Amongst the 19 patients in the prevention group, 14 (70.4%) received mycophenolate derivatives at the start of ECP and last reported visit. In 4/14 patients, mycophenolate doses were available of which 100% of patients remained on stable mycophenolate derivate dose.
- Seventeen of 105 included patients (16.2%) experienced a complication after ECP treatment initiation, the most common of which was infections (n=13, 12.4%). Four of 105 patients (3.8%) experienced an endocrine/respiratory/blood/cardiac disorder, 2 patients (1.9%) an intolerance of high-dose immunosuppressive therapy, and 1 patient (1.0%) an acute kidney injury.
- Overall survival was 95.2% (n=100) over a mean follow-up of 25.1 (SD 16.8) months. Of the 5 deceased patients, 3 (60.0%) died with a functioning graft and 4 (80.0%) died after end of ECP treatment. No deaths were related to ECP.
- No major safety events occurred. Eighteen of 105 included patients (17.1%) had at least one ECP-related safety event, the most common of which was complications with venous access (n=13; 12.4%). Two (15.4%, n=2/13) patients stopped their ECP treatment as a result. Furthermore, 6/105 patients (5.7%) had ECP-related anemia, 3 patients (2.9%) ECP-related hypotension, 1 patient (1.0%) ECP-related fever, and 2 patients (1.9%) had an unspecified ECP-related safety event, but none of them discontinued their ECP treatment as a result.

Limitations[1]

The effectiveness of ECP in comparison with other treatment options was not assessed due to the descriptive, single-arm design of this study. Study limitations include that data generation for this observational study was not standardized. Patient examination schedules varied and not all data were available at all centers. No source data verification was performed and therefore, transmission errors cannot be excluded. Not all demonstrated benefits may be solely attributable to ECP treatment, as transplanted patients may have received multiple therapies at time of ECP treatment. In patients with AMR or mixed rejection, ECP is commonly used in combination with other treatments.

This study was funded by Mallinckrodt.

IMPORTANT SAFETY INFORMATION FOR THE THERAKOS™ PHOTOPHERESIS PROCEDURE

Indications
The THERAKOS™ CELLEX™ Photopheresis System is indicated for the administration of photopheresis. Please refer to the appropriate product labelling for a complete list of warnings and precautions.

Contraindications
THERAKOS™ Photopheresis is contraindicated in:

- Patients possessing a specific history of light sensitive disease
- Patients who cannot tolerate extracorporeal volume loss or who have white blood cell counts greater than 25,000 / mm^3
- Patients who have coagulation disorders or who have previously had a splenectomy

Warnings and Precautions
THERAKOS™ Photopheresis treatments should always be performed in locations where standard medical emergency equipment is available. Volume replacement fluids and/or volume expanders should be readily available throughout the procedure. Safety in children has not been established.

- Do not expose the device to a magnetic resonance (MR) environment. The device may present a risk of protective injury, and thermal injury and burns may occur. The device may generate artifacts in the MR image, or may not function properly.
- Thromboembolic events, including pulmonary embolism and deep vein thrombosis, have been reported in the treatment of Graft versus Host Disease (GvHD). Special attention to adequate anticoagulation is advised when treating patients with GvHD.
- When prescribing and administering THERAKOS Photopheresis for patients receiving concomitant therapy, exercise caution when changing treatment schedules to avoid increased disease activity that may be caused by abrupt withdrawal of previous therapy.

Adverse Events

- Hypotension may occur during any treatment involving extracorporeal circulation. Closely monitor the patient during the entire treatment for hypotension.
- Transient pyretic reactions, 37.7–38.9 °C (100–102 °F), have been observed in some patients within six to eight hours of reinfusion of the photoactivated leukocyte-enriched blood. A temporary increase in erythroderma may accompany the pyretic reaction.
- Treatment frequency exceeding labelling recommendations may result in anaemia.
- Venous access carries a small risk of infection and pain.

Please refer to the THERAKOS™ CELLEX™ Photopheresis System Operator Manual for a complete list of warnings and precautions.

IMPORTANT SAFETY INFORMATION FOR METHOXSALEN USED IN CONJUNCTION WITH THERAKOS™ PHOTOPHERESIS

Contraindications
Methoxsalen is contraindicated in:

- Patients exhibiting idiosyncratic or hypersensitivity reactions to methoxsalen, psoralen compounds, or any of the excipients
- Patients with co-existing melanoma, basal cell or squamous cell skin carcinoma
- Patients who are pregnant, and sexually active men and women of childbearing potential unless adequate contraception is used during treatment
- Patients with aphakia because of the significantly increased risk of retinal damage to the absence of a lens

Warnings and Precautions

- Special care should be exercised in treating patients who are receiving concomitant therapy (either topically or systemically) with known photosynthesizing agents.
- Oral administration of methoxsalen followed by cutaneous UVA exposure (PUVA therapy) is carcinogenic**.**
- Patients should be told emphatically to wear UVA absorbing, wrap-around sunglasses for twenty-four (24) hours after methoxsalen treatment. They should wear these glasses anytime they are exposed to direct or indirect sunlight, whether they are outdoors or exposed through a window.
- Safety in children has not been established.

Refer to the package insert for methoxsalen sterile solution (20 micrograms / mL) or the oral 8-methoxpsoralen dosage formulation for a list of all warnings and precautions.

Please refer to the THERAKOS™ CELLEX™ Photopheresis System Operator Manual for a complete list of warnings and precautions and adverse events.

About Extracorporeal Photopheresis (ECP)
ECP, a blood based immunomodulatory therapy developed more than 30 years ago, is recommended by the International Society for Heart and Lung Transplantation (ISHLT)[3] and other clinical societies[4,5,6] as an adjunctive therapy for the prevention and treatment of ACR after heart transplantation. Additionally, ECP may be considered to treat AMR with or without donor specific antibodies.[7,8] In countries where it is approved, ECP is used to treat a range of immune-mediated diseases, including skin manifestations of cutaneous T-cell lymphoma (CTCL), graft-versus-host disease (GvHD), solid organ transplant rejection and other autoimmune diseases. During ECP treatment, a small amount of white blood cells is collected and treated with a drug that is activated by ultraviolet light.

ABOUT MALLINCKRODT
Mallinckrodt is a global business consisting of multiple wholly owned subsidiaries that develop, manufacture, market and distribute specialty pharmaceutical products and therapies. The company's Specialty Brands reportable segment's areas of focus include autoimmune and rare diseases in specialty areas like neurology, rheumatology, hepatology, nephrology, pulmonology, ophthalmology, and oncology; immunotherapy and neonatal respiratory critical care therapies; analgesics; cultured skin substitutes and gastrointestinal products. Its Specialty Generics reportable segment includes specialty generic drugs and active pharmaceutical ingredients. To learn more about Mallinckrodt, visit www.mallinckrodt.com.

Mallinckrodt uses its website as a channel of distribution of important company information, such as press releases, investor presentations and other financial information. It also uses its website to expedite public access to time-critical information regarding the company in advance of or in lieu of distributing a press release or a filing with the U.S. Securities and Exchange Commission (SEC) disclosing the same information. Therefore, investors should look to the Investor Relations page of the website for important and time-critical information. Visitors to the website can also register to receive automatic e-mail and other notifications alerting them when new information is made available on the Investor Relations page of the website.

CAUTIONARY STATEMENTS RELATED TO FORWARD-LOOKING STATEMENTS
This release contains forward-looking statements, including with regard to ECP and its potential impact on patients. The statements are based on assumptions about many important factors, including the following, which could cause actual results to differ materially from those in the forward-looking statements: satisfaction of regulatory and other requirements; actions of regulatory bodies and other governmental authorities; changes in laws and regulations; issues with product quality, manufacturing or supply, or patient safety issues; and other risks identified and described in more detail in the "Risk Factors" section of Mallinckrodt's most recent Annual Report on Form 10-K and other filings with the SEC, all of which are available on its website. The forward-looking statements made herein speak only as of the date hereof and Mallinckrodt does not assume any obligation to update or revise any forward-looking statement, whether as a result of new information, future events and developments or otherwise, except as required by law.

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