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PRESS RELEASE

Using Stem Cells Against Chronic Venous Ulcers (CVU)

Potential identified: Independent expert committee advocates finalization of a phase IIb clinical trial of ABCB5+ mesenchymal stromal cells in treating CVU

Heidelberg, March 21, 2024. RHEACELL – the biopharmaceutical company – has received a positive vote from the IDMC[1] (Independent Data Monitoring Committee) for a phase IIb trial to investigate ABCB5+ mesenchymal stromal cells (MSCs) in treating chronic venous wounds. The commissioned expert committee responsible for independent data monitoring of blinded clinical trials, with this positive recommendation to accelerate finalization of the trial, underlines the potential of the cell therapy for treating refractory chronic venous wounds – a disease with a high demand for medical treatment. MSCs were also an important topic at the press conference at *DERMATOLOGIE kompakt + praxisnah 2024* meeting in Wiesbaden, where this innovative therapeutic approach was presented.

Ulcus cruris (“leg sores”) is a chronic ulcer on the lower leg that only heals slowly or not at all. In Germany, the prevalence of florid chronic ulceration is 0.7% of the population. (1) Chronic venous ulcers (CVU) make up the majority of chronic wounds. The quality of life of those affected is significantly restricted by complex, repeated wound treatments and pain. So far, there have been no adequate treatment options, particularly for severely affected patients with a therapy-refractory course. (2-5)

Healing of chronic wounds is impaired by stagnation of the inflammation phase of wound healing. This leads to overactivation of type-1 macrophages, which prevents the transition from the inflammatory phase to the subsequent phase of wound healing, regeneration with the deposition of collagen, and the formation of new skin tissue.

Innovative stem cell research: Hope for those with chronic venous wounds?

Skin-derived ABCB5+ mesenchymal stromal cells (MSCs) have unique immunomodulatory properties, including the release of interleukin (IL)-1RA. This binds to the receptor and thus inhibits cytokine IL-1β. Applied topically, the MSCs nest themselves in the wound and interact with the surrounding

[1] www.ema.europa.eu/en/documents/scientific-guideline/guideline-data-monitoring-committees_en.pdf

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immune cells. This way they reprogram the change from pro-inflammatory M1 macrophages to healing-promoting M2 macrophages and support the body in the self-healing process. (6-7)

In a phase IIa clinical trial in patients with CVU, it had already been demonstrated that ABCB5+ MSCs have the potential to improve wound healing and contribute to the healing of chronic wounds. Based on the available data, in 2021 the Paul-Ehrlich-Institut (PEI) granted the innovative cell therapy national marketing authorization for use in specialized clinics for treating patients with therapy-refractory CVU. (8)

Positive IDMC vote: Independent expert committee approves accelerated finalization of the phase IIb clinical trial

The efficacy and safety of the cell therapy is currently under further investigation in an ongoing, randomized, placebo-controlled phase IIb trial for treating CVU. Wound treatment with ABCB5+ MSCs has been investigated in three different dose groups compared with placebo in a total of 102 study participants so far. Thanks to its access to unblinded data from the study, the expert IDMC commissioned is in a position to make far-reaching recommendations to the pharmaceutical manufacturer: After evaluating the initial data, the committee recommended only continuing one of the three original dose groups. This means that the preferred dosage (1 million ABCB5+ MSCs/cm^2), which also forms the basis for the preliminary PEI marketing authorization, appears to be able to meet or exceed the assumed effect as compared to the placebo.

Dr. med. Andreas Kerstan, Associate Professor from Würzburg, head of the CVU phase IIb trial, on his interpretation of the IDMC recommendation: *"The positive feedback from the IDMC represents a milestone in the trial and was based on the preliminary results. They show a 3-fold improvement in wound healing in patients treated with MSCs as compared to the placebo group; at least 30% more patients achieved wound closure with the cell therapy. By eliminating the two non-preferred dose groups, only 50 additional participants need to be recruited and randomized 1:1 against placebo to complete the phase IIb trial. This is expected to lead to early completion of this clinically important trial."*

High demand for treating CVU: Experts welcome IDMC recommendation

Professor Dr. med. Karin Scharffetter-Kochanek (Ulm), who has played a leading role in the preclinical and clinical research of ABCB5+ MSCs from the very outset, is delighted with the IDMC vote: *"Anything that can contribute to rapid, data-based authorization of the innovative stem cell therapy is a real step forward in view of the high demand of our patients for therapy.*

Chronic venous ulcers occur in 2 to 5% of patients over 60 years of age. The development of effective therapeutic options for these age-related diseases is important. In line with the age demographics, our society must prepare for

more older people with chronic wounds, a demand that we can hardly meet today due to treatment-refractory courses.", according to Scharffetter-Kochanek.

Despite intensive research, only a few stem cell therapies have so far advanced to clinical application. The cell therapy (as a pre-filled syringe with 5 million ABCB5+ MSCs) is only the second mesenchymal stem cell product to receive national marketing authorization. This cell therapy has already been available in specialized clinics for treating therapy-refractory CVU patients for two years. This therapeutic option in everyday clinical practice exists in parallel with continuing randomized clinical trials.

Dr. Galina Balakirski, senior physician and medical wound expert *ICW/TÜV* (a German professional association dedicated to improving wound care and healing) at the Center for Dermatology, Allergology and Dermatosurgery, Helios University Hospital in Wuppertal, is already convinced of the good effectiveness in practice: *"My impression of the drug is very good. Several patients report rapid pain relief. In all likelihood, we now have a very effective therapeutic agent for treating therapy-refractory wounds*", Balakirski asserts.

Therapy concept presented at press conference of the *DERMATOLOGIE kompakt + praxisnah (KoPra)* meeting

Due to the high medical demand and the optimistic data situation, the German Dermatological Society (*DDG*) addressed the topic at its opening press conference at this year's *KoPra* meeting on March 1, 2024. Professor Dr. med. Silke Hofmann (Director of the Center for Dermatology, Allergology and Dermatosurgery, Helios University Hospital in Wuppertal and *DDG* Public Relations Officer) explained in her lecture "New therapy concepts for chronic wounds: *Activating the body's own repair mechanisms with human skin stem cells"* the innovative approach of ABCB5+ MSCs.

With a view to the phase I/IIa trial results and the initial practical experience in her clinic, she summarized: "*The treatment was successful and well tolerated, and makes ABCB5+ mesenchymal stem cells a candidate for complementary therapy of otherwise incurable CVU*". The speaker's conclusion: MSCs have great potential – also for other diseases such as epidermolysis bullosa (butterfly disease). (9, 10)

References:

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[7] Kerstan A et al. JID Innovations 2022;2:100067.

[8] Gebrauchs- und Fachinformation AMESANAR®

[9] https://www.derma-tagungen.de/release/kopra2024/de-DE/page/Presse

[10] Link to the video recording (in German) of the *DDG* press conference at *KoPra 2024*: https://www.rheacell.com/de/aktuelles/

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About RHEACELL

With over 15 years of experience, we are a leading integrative biopharmaceutical stem cell company with authorization trials, based in Heidelberg, Germany. We focus on innovative stem cell therapies for patients suffering from severe inflammation-driven diseases with high unmet medical need and to provide a new and innovative standard of care for these patients, who currently have no satisfactory treatment options available.

Our ABCB5+ mesenchymal stromal cells as pure drug substance can make a real difference for the lives of these patients, e.g., in Epidermolysis Bullosa, having the potential to be a real game changer.

We develop clinical research programs hand in hand with world-leading experts, focusing on patients with unmet medical needs, e.g., in rare pediatric and dermatological diseases accompanied by and/or based on systemic inflammation.

Based on the mode of action and relevant potency assays, RHEACELL has a significant pipeline to further broaden its clinical development and market access into other rare and orphan diseases. We conduct several national and international multicenter late-stage clinical trials.

The cell therapy targets inflammation and is enabling recovery of normal physiological function and initiating neo-vascularization after topical application.

In our pharmaceutical production based on validated safety and efficacy tests, we have full control over all crucial steps, from production to release of the medicinal product, thus guaranteeing the best pharmaceutical quality. Our GMP-certified manufacturing process is always scalable to meet global demand.

We hold world-wide IP protection by a comprehensive patent portfolio on ABCB5, exclusively licensed by RHEACELL from Children's and Women's Hospital, Harvard Medical School, Boston, several of these co-owned by RHEACELL, and the proprietary in -house know-how gives us a competitive advantage in the industry.