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TRECONDI[®] (treosulfan) by medac received EU-wide approval for toxicity-reducing conditioning therapy prior to allogeneic haematopoietic stem cell transplantation

medac was granted a marketing authorisation by the European Commission for TRECONDI[®] (treosulfan), as part of conditioning treatment prior to alloHSCT in adult patients with malignant and non-malignant diseases and in paediatric patients with malignant diseases

Wedel (25 June 2019). German pharmaceutical company medac Gesellschaft für klinische Spezialpräparate mbH today announced that the European Commission (EC) has granted marketing authorisation for TRECONDI[®] (treosulfan) in combination with fludarabine as part of conditioning treatment prior to allogeneic haematopoietic stem cell transplantation (alloHSCT) in adult patients with malignant and non-malignant diseases and in paediatric patients older than one month with malignant diseases. The EC approval is essentially based on data from the pivotal Phase 3 study MC-FludT.14/L-Part II¹ and the Phase 2 study MC-FludT.17/M². The successful development and approval of this new toxicity-reduced conditioning regimen with TRECONDI[®] strengthens medac's position in the field of haematology. The decision takes effect for all 28 EU Member States plus Liechtenstein, Iceland, and Norway where TRECONDI[®] is about to be launched.

¹ EU Clinical Trials Register, Clinical phase III trial to compare Treosulfan-based conditioning therapy with Busulfan-based reduced-intensity conditioning (RIC) prior to allogeneic haematopoietic stem cell transplantation in patients with AML or MDS considered ineligible to standard conditioning regimens. EudraCT Number: 2008-002356-18.

² EU Clinical Trials Register, Clinical phase II trial to describe the safety and efficacy of Treosulfan-based conditioning therapy prior to allogeneic haematopoietic stem cell transplantation in paediatric patients with haematological malignancies. EudraCT Number: 2013-003604-39.

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Conditioning with treosulfan – clinically relevant survival benefit

Allogeneic haematopoietic stem cell transplantation (alloHSCT) is the only potentially curative treatment option for many malignant and non-malignant diseases.³ It is imperative that transplantation be preceded by preparatory conditioning therapies. The standard in this respect is conditioning with high-dose, toxic myeloablative regimes which, however, are not suitable for numerous at-risk groups.⁴ For some time now, research has therefore been conducted into so-called reduced-intensity conditioning therapies.^{4,5} With the treosulfan-based reduced-toxicity conditioning (RTC) by medac, such a new therapy option is approved now Europe-wide. The treosulfan-based treatment is characterised by a high level of intensity and antileukaemic effect comparable to that of the myeloablative regimens with considerably reduced toxicity at the same time.^{6,7,8}

The approval takes into account the current study data for TRECONDI[®], register data as well as the extensive literature and confirms the efficacy and safety of the treosulfan-based conditioning regimen with its low toxicity profile. This will benefit at-risk groups in particular, who are excluded from the myeloablative regimens.

³ Niederwieser D et al. Hematopoietic stem cell transplantation activity worldwide in 2012 and a SWOT analysis of the Worldwide Network for Blood and Marrow Transplantation Group including the global survey. *Bone Marrow Transplant.* 2016;51:778-785.

⁴ Bacigalupo A et al. Defining the intensity of conditioning regimens: working definitions. *Biol Blood Marrow Transplant.* 2009;15:1628-1633.

⁵ Sakellari I et al. Survival Advantage and Comparable Toxicity in Reduced-Toxicity Treosulfan-Based versus Reduced-Intensity Busulfan-Based Conditioning Regimen in Myelodysplastic Syndrome and Acute Myeloid Leukemia Patients after Allogeneic Hematopoietic Cell Transplantation. *Biol Blood Marrow Transplant.* 2017;23:445-451.

⁶ Ruutu T et al. Reduced-toxicity conditioning with treosulfan and fludarabine in allogeneic hematopoietic stem cell transplantation for myelodysplastic syndromes: final results of an international prospective phase II trial. *Haematologica.* 2011;96:1344-1350.

⁷ Casper J et al. Allogeneic hematopoietic SCT in patients with AML following treosulfan/fludarabine conditioning. *Bone Marrow Transplantation.* 2012;47:1171-1177.

⁸ Shimoni A et al. Allo-SCT for AML and MDS with treosulfan compared with BU-based regimens: reduced toxicity vs reduced intensity. *Bone Marrow Transplant.* 2012;47:1274-1282.

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MC-FludT.14/L-Part II Phase 3 study¹ on adult patients

The MC-FludT.14/L study to date is the largest international prospective Phase 3 study on conditioning treatment with treosulfan. It investigated a treosulfan/fludarabine-based conditioning regimen with 3×10 g/m² treosulfan as an alternative to reduced-intensity conditioning therapy with busulfan/fludarabine in 570 predominantly elderly patients with acute myeloid leukaemia (AML) and myelodysplastic syndrome (MDS)⁹, who sometimes had comorbidities, and for whom allogeneic HSCT was indicated.^{10,11,12,13} In addition to the early achievement of the primary endpoint, the study notably yielded excellent results for the secondary endpoints, particularly in terms of survival. For example, event-free survival (EFS) in the treosulfan group after 2 years was significantly higher at 65.7% than 51.2% for the busulfan-based control group.

⁹ The median age of patients was 60 years (range 31–70 years), 25% of patients were older than 65 years. 64% of patients had AML and 36% MDS.

¹⁰ Beelen, DW et al., Final Results of a Prospective Randomized Multicenter Phase III Trial Comparing Treosulfan / Fludarabine to Reduced Intensity Conditioning with Busulfan / Fludarabine Prior to Allogeneic Hematopoietic Stem Cell Transplantation in Elderly or Comorbid Patients with Acute Myeloid Leukemia or Myelodysplastic Syndrome. *Blood*. 2017;130 (Suppl 1):521. URL: http://www.bloodjournal.org/content/130/Suppl_1/521 (Stand: 25.06.2019).

¹¹ Beelen DW. et al., Results of a randomized phase III trial comparing treosulfan/fludarabine to reduced-intensity conditioning with busulfan/fludarabine before allogeneic hematopoietic stem cell transplantation in acute myeloid leukemia or myelodysplastic syndrome. Oral abstract #OS8-2. 2018 European Society for Blood and Marrow Transplantation (EBMT) Annual Meeting, Lisbon.

¹² Beelen DW. et al., Final Evaluation of a Clinical Phase III Trial Comparing Treosulfan to Busulfan-Based Conditioning Therapy Prior to Allogeneic Hematopoietic Stem Cell Transplantation of Adult Acute Myeloid Leukemia and Myelodysplastic Syndrome Patients Ineligible to Standard Myeloablative Regimens. *Biol Blood Marrow Transplant*. 2019;25 (Suppl):S3

¹³ Beelen DW. et al., Improved survival of AML and MDS patients after treosulfan-based conditioning and allogeneic haematopoietic cell transplantation. Final results of a prospectively randomised phase III trial comparing treosulfan- with reduced-intensity busulfan-based conditioning treatment. Presidential Symposium #GS2-1. 2019 European Society for Blood and Marrow Transplantation (EBMT) Annual Meeting, Frankfurt.

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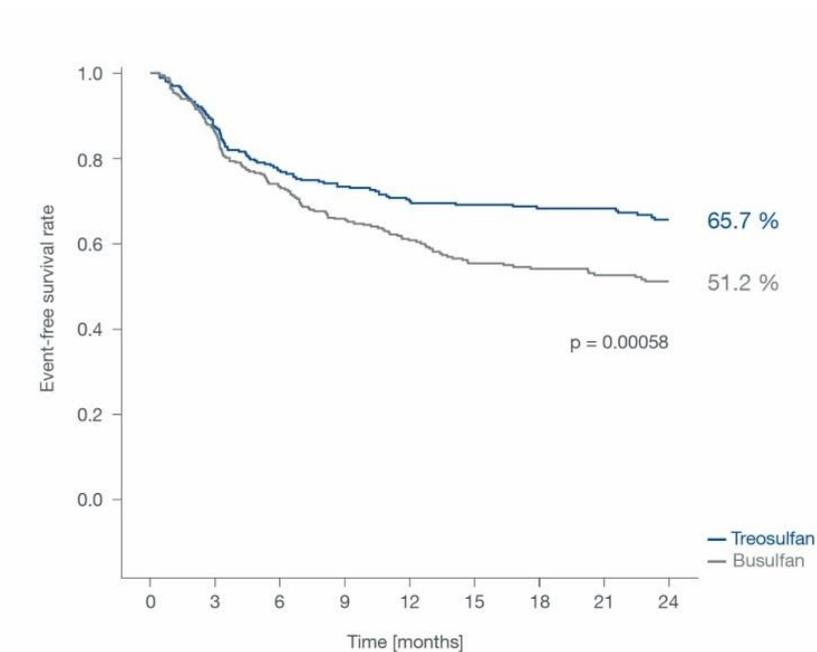


Figure: Event-free survival after conditioning with treosulfan vs. busulfan up to 24 months, © medac

At the same time, overall survival (OS) on the treosulfan-based regimen was also considerably higher than in the busulfan comparator arm, at 72.7% vs. 60.2%. The conditioning therapy with treosulfan-based regimen for MDS and AML thus shows a survival rate of more than 70% after two years.

Effective and well-tolerated in adult patients with non-malignant diseases

The treosulfan-based conditioning regimen also results in highly favourable outcomes when used for other indications, although the data are not so extensive available on treosulfan-based conditioning in adult patients with non-malignant disorders (NMD).^{14,15,16,17} The main indications for an alloHSCT

¹⁴ Burroughs LM et al., Treosulfan-based conditioning and hematopoietic cell transplantation for nonmalignant diseases: a prospective multicenter trial. *Biol Blood Marrow Transplant.* 2014;20:1996-2003.

¹⁵ Bernardo ME et al., Allogeneic hematopoietic stem cell transplantation in thalassemia major: results of a reduced-toxicity conditioning regimen based on the use of treosulfan. *Blood* 2012;120:473-476.

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with treosulfan conditioning in adult NMD patients are haemoglobinopathies (e.g. sickle cell disease, thalassaemia major and Fanconi's anaemia), primary immune deficiency, hemophagocytic disorder, immune dysregulatory disorder and bone marrow failure.

MC-FludT.17/M Phase 2 study² on paediatric patients

A Phase 2 study with 70 paediatric patients aged from 28 days to 18 years also confirmed the high level of efficacy and safety of conditioning with treosulfan in children with malignant blood diseases. In particular, the good results regarding the non-relapse mortality rate (NRM) favour the use of treosulfan-based conditioning therapy in children.¹⁸ The maximum conditional cumulative engraftment rate of 100% is excellent. In this study 98.6% reached the primary endpoint freedom from transplant-related mortality (TRM) 100 days after HSCT.

Treosulfan – About the active substance and mode of action

The active compound treosulfan is a prodrug and belongs to the group of bifunctional alkylating agents. Despite its structural similarity to busulfan, the treosulfan molecule shows a different mechanism of action due to its two hydroxyl groups. Under physiological conditions, an enzyme-independent intramolecular nucleophilic substitution takes place. Formation of an epoxide ring results in the elimination of two methane sulphonic acid molecules. The resulting molecules (1,2-epoxy-3,4-butanediol-4-methane sulfonate and L-diepoxybutane) are to be regarded as the chemically effective reaction products which bind to biological macromolecules and trigger the antiproliferative and cytotoxic effect.

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¹⁶ Mathews V et al., Improved clinical outcomes of high risk β thalassemia major patients undergoing a HLA matched related allogeneic stem cell transplant with a treosulfan based conditioning regimen and peripheral blood stem cell grafts. *PLoS One*. 2013;8:e61637.

¹⁷ Caocci G et al., Long-term survival of beta thalassemia major patients treated with hematopoietic stem cell transplantation compared with survival with conventional treatment. *American Journal of Hematology* 2017;92:1303-1310.

¹⁸ Kalwak, K et al. Prospective Clinical Phase II Results on Treosulfan-Based Conditioning Treatment of 70 Paediatric Patients with Haematological Malignancies. *Blood*. 2018;132 (Suppl 1):3354. URL: http://www.bloodjournal.org/content/132/Suppl_1/3354 (Stand: 25.06.2019).

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medac is a privately-owned German pharmaceutical company with sites in Wedel and Tornesch. medac's medicinal products are used worldwide to help doctors and patients manage acute and chronic diseases in the fields of oncology and haematology, urology, and autoimmune diseases. medac also develops and distributes specialist diagnostic systems. Since 1970, medac has been committed to its approach of uniting therapeutic and diagnostic products under one roof. Further information on the company and its products can be found online at www.medac.de.