New conditioning therapy by medac about to receive European approval

Positive opinion from the CHMP for TRECONDI® (treosulfan) by medac for toxicity-reducing conditioning for allogeneic haematopoietic stem cell transplantation

- Highly effective with reduced toxicity - Treosulfan-based regimen is the new conditioning therapy for malignant and non-malignant diseases
- The MC-FludT.14/L phase III study data found a considerably higher overall survival rate in adults with a treosulfan-based reduced-toxicity conditioning treatment prior to allo-HSCT with 71.3% at 24 months as compared to busulfan¹,²
- The MC-FludT.17/M phase II study also found a treosulfan-based conditioning treatment to be safe and effective in children and adolescents³,⁴

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² 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: 12.12.2018).
Wedel, 14 December 2018. medac Gesellschaft für klinische Spezialpräparate mbH announced today that the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has issued a positive opinion for the approval of TRECONDI® (treosulfan) in combination with fludarabine as part of conditioning treatment prior to allogeneic haematopoietic stem cell transplantation in adult patients with malignant and non-malignant diseases, and in paediatric patients older than one month with malignant diseases. The CHMP opinion is essentially based on the results of the pivotal MC-FludT.14/L-Part II phase III study and the MC-FludT.17/M phase II study.1,3 The CHMP opinion will now be reviewed by the European Commission, which is authorised to approve medicinal products within the European Union. Its decision will then take effect for all 28 EU Member States plus Liechtenstein, Iceland, and Norway.

**Conditioning with treosulfan – clinically relevant survival benefit**

Allogeneic haematopoietic stem cell transplantation (allo-HSCT) is the only potentially curative treatment option for many malignant and non-malignant diseases.5 It is imperative that transplantation be preceded by preparatory conditioning therapies. The standard in this respect is conditioning with high-dose, toxic myeloablative regimens which, however, are not suitable for numerous at-risk groups.6 For some time now, research has therefore been conducted into so-called reduced-intensity conditioning therapies.6,7 With the treosulfan-based reduced-toxicity conditioning (RTC) by medac, just such a new therapy option is about to be approved. The treosulfan-based treatment is characterised

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by a high level of intensity and antileukaemic effect comparable to that of the myeloablative regimens with considerably reduced toxicity at the same time.\textsuperscript{8,9,10}

The positive CHMP opinion takes into account the current study data for TRECONDI\textsuperscript{®} 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 currently established myeloablative regimens.

**MC-FludT.14/L-Part II phase III study**

To date the largest international prospective phase III study on conditioning treatment with treosulfan, this study investigated a treosulfan/fludarabine-based conditioning regimen as an alternative to reduced-intensity conditioning therapy with busulfan/fludarabine in 476 predominantly elderly and in some cases comorbid patients with acute myeloid leukaemia (AML) and myelodysplastic syndrome (MDS) in which allogeneic HSCT was indicated.\textsuperscript{1} In addition to the early achievement of the primary study objective, the study results are also noteworthy for the outstanding results of the secondary endpoints, particularly concerning the overall survival and transplant-related mortality (TRM). The overall survival in the treosulfan group was considerably higher at 71.3\% than in the busulfan-based conditioning therapy group at 56.4\%. At the same time, the TRM for the treosulfan-based regimen was 12.1\%, and therefore significantly lower than the 28.2\% for the busulfan comparator arm.\textsuperscript{2,11}


\textsuperscript{10} 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.

\textsuperscript{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. European Society for Blood and Marrow Transplantation (EBMT) Annual Meeting 2018, Lisbon, Oral abstract #OS8-2.
MC-FludT.17/M phase II study

A phase II 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.3 In particular, the good results regarding the non-relapse mortality rate (NRM) favour the use of treosulfan-based conditioning therapy in children.4

Treosulfan – 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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Press release

14-Dec-2018

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