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ORIGINAL ARTICLE

Efficacy and Tolerability of a 2-Year Rituximab Maintenance Therapy in Patients with Advanced Follicular Lymphoma after Induction of Response with Rituximab-Containing First Line-Regimens (HUSOM Study)

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Abstract Follicular lymphoma is a lymphoid malignancy commonly showing slow progression which makes the treatment of the disease challenging. Rituximab monotherapy and rituximab added to standard chemotherapy has been proven to increase survival among patients with advanced stage of the disease. However, the benefit of a rituximab maintenance therapy after induction was still unclear at the time of the initiation of this study. HUSOM was a phase III open-label, single-arm, multi-centre study aimed to assess the efficacy and the safety of the 12 cycles of rituximab (375 mg/m^2 every 8 weeks) maintenance therapy in patients had already presented partial or complete response to R-CVP or R-CHOP. Efficacy endpoints such as event-free survival and overall survival were estimated. Adverse events were recorded during the entire course of the study. A total number of 124 patients were enrolled by 15 Hungarian study sites. Out of these, 86 patients received 12 cycles of rituximab and 69 patients completed the 3-year follow-up phase as well. The probabilities of the event free survival and progression at 4.3 years were estimated to be 70.3% and 74.4%, respectively. The overall and the disease free survival at 4 years were estimated to be 90.7% and 87.9%, respectively. A total number of 85 adverse events were reported during the study out of which 5 AEs were considered to be related to the administration of rituximab. Analyses of the

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efficacy variables have revealed comparable results to those reported by controlled clinical trials (EORTC 20981, PRIMA) conducted in parallel with the HUSOM study.

Keywords Follicular lymphoma · Rituximab · Maintenance · Event-free survival · Drug safety

Introduction

Follicular lymphoma (FL) belongs to a group of diseases known collectively as non-Hodgkin's lymphomas (NHLs). These malignancies affect lymphoid tissues (mainly lymph nodes) eventually resulting in uncontrolled replication of lymphocytes. The incidence of FL is similar in men and women and increases with age: rates increase sharply in people over 50 and around two-thirds of all cases are diagnosed in people over 60 years of age [1].

The clinical course of indolent FL is characterized by cycles of relapses and remissions. Since the disease is incurable with the currently available treatment options, the majority of patients die after multiple remissions and subsequent relapses. The median survival in this patient population is between 6 and 10 years. Besides the standard chemotherapy, monoclonal antibodies with immunomodulatory effect have also gained importance in the first line treatment of FL [2, 3].

Rituximab is a chimeric murine/human monoclonal antibody that is directed specifically against the B-cell antigen CD20 [4]. Rituximab was shown to induce both complement-mediated and antibody-dependent cell-mediated lysis of CD20+ cells [5], moreover sensitization of drug-resistant human B-cell lymphoma cell lines to cytotoxic agents has also been observed [6]. Clinical data showed the rapid depletion of CD20+ B-cells 24–72 h after rituximab administration. This effect was apparent even after 2–3 months of therapy [7].

Clinical trials evaluating single-agent rituximab in indolent NHL have been conducted primarily in patients with relapsed or refractory disease. Early phase I/II trials showed an overall response rate of 33%–50% with the absence of dose limiting side-effects [8]. A number of phase II or randomized phase III studies have demonstrated the efficacy of rituximab when added to various chemotherapy regimens such as CHOP [9–11], CVP [12] or fludarabine based regimens [13–17] for the first line treatment of FL without adding significant toxicity.

The most frequent adverse events reported in relation with rituximab therapy primarily included fever, chills, headache, nausea, vomiting, rhinitis, mild hypotension, neutropenia, thrombocytopenia and asthenia [18, 19].

Despite the high response rates observed in follicular NHL patients receiving regimens containing add-on rituximab, the pattern of continuous relapse among responder patients remains problematic. Clinical evidences showed that patients previously responding to rituximab may respond to a second course of therapy [20]. Additional phase II and phase III trials have confirmed that prolonged exposure to rituximab monotherapy improves clinical results in terms of EFS, response duration and proportion of patients still in response at one year [21–23].

It was therefore required to investigate, whether maintenance treatment with rituximab could further improve the outcome of patients with FL who previously responded to a rituximab-containing first line induction treatment.

Materials and Methods

Study Design and Patients

This phase III open-label, single-arm, multi-centre study was designed to assess the efficacy and safety of a long-term rituximab in patients with advanced follicular lymphoma after induction of clinical response with a rituximab-containing first line regimen.

Adult follicular lymphoma patients (i.e. histologically confirmed grade 1, 2 or 3a) with complete (CR(u)) or partial (PR) response to a predefined rituximab-containing first line regimen eligible were sought for enrollment. Eligible first line induction regimens included 8 cycles of cyclophosphamide, vincristine, and prednisone (CVP) or 6–8 cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) both combined with 8 cycles of rituximab (R-CVP, R-CHOP). Lymph node biopsy had to be performed within 4 months before the induction treatment.

Additional eligibility criteria included a life expectancy of longer than 4 months; documented parameters for FLIPI determination before induction therapy, ECOG status of 0, 1 or 2; acceptable haematological status (i.e. haemoglobin (Hb) > 8 g/dl, white blood cell (WBC) count >3.0 × 10^3/mm^3 (× 10^9/l), absolute granulocyte count >1.5 × 10^3/mm^3 (× 10^9/l), platelet count >75 × 10^3/mm^3 (× 10^9/l)) within two weeks prior to treatment start; agree to follow accepted birth control methods during the trial.

Patients who had grade 3B lymphomas, previous antilymphoma treatments other than first-line R-CVP or C-CHOP, CNS lymphoma, HIV, HBV or HCV infections, hepatic or renal impairment were excluded from the study population. All patients were required to provide written informed consent before entering the study.

Between July 2005 and December 2008, a total number of 124 (40 males and 84 females) patients were found eligible for participation in the study as fulfilled all inclusion criteria and thus were enrolled by 15 clinical centres in Hungary. The median age of the patients was 53.7 years (range: 26.3–81.3 years), whereas the median height and weight of the enrolled subjects were 167 cm (range: 150–193 cm) and 75 kg (range: 44–120 kg), respectively. The median age of female patients (55 years) were somewhat higher compared

to the median age of male subjects (50 years). At baseline, approximately half of the patients (63 patients, 50.8%) were grade 2 according to the histological criteria, whereas the grading of the remaining patients were almost equally distributed between grade 1 (34 patients, 27.4%) and grade 3a (27 patients, 21.8%). At baseline, the majority of the patients showed normal laboratory values except 3 patients having grade 3 deviation in neutrophil granulocyte status and 1–1 patient having grade 3 deviation in uric acid and serum LDH levels, respectively.

Treatment

Eligible subjects received 12 cycles of rituximab infusion (375 mg/m^2 every 8 weeks) as a maintenance treatment. The maximum allowed period between the last infusion of the induction and first infusion of rituximab maintenance therapy was 8 weeks. Rituximab was reconstituted in an infusion bag containing either 0.9% sodium chloride or 5% dextrose by using aseptic technique. The first rituximab infusion of each induction therapy cycle was administered at an initial rate of 50 mg/h. If no hypersensitivity or infusion-related reactions occurred, the rate of the infusion could be increased by 50 mg/h increments at 30-min intervals to a maximum rate of 400 mg/h. If hypersensitivity (non-IgE-mediated) or an infusion-related reaction developed, the infusion was temporarily slowed or interrupted. The infusion could continue at one-half the previous rate upon improvement of the patient's symptoms. Anti-histamines and paracetamol and optionally pethidine were allowed to administer in case of serious infusion-related adverse event.

Because the risk of developing hypersensitivity reactions to rituximab, all patients were pre-medicated with oral acetaminophen and diphenhydramine and according to institutional practice approximately 30 min prior to each dose of rituximab. Patients received full supportive care, including transfusions of blood and blood products, antibiotics, anti-emetics, and hematopoietic colony-stimulating factors (G-CSF, GM-CSF) according to routine clinical practice.

Procedures

Before beginning therapy, all patients underwent staging procedures including history, physical examination, complete blood counts, chemistry profile, tumor biopsy and histology, computerized tomography of the chest and abdomen and bone marrow biopsy. Disease progression was evaluated according to the Ann Arbor staging subclassification system at screening, at the end of the maintenance therapy and at the end of the follow-up phase. Tumour staging was based on the results of bone marrow biopsy, lesion assessments and imaging examinations (i.e. X-ray, CT and/or MR of the chest and abdomen).

Moreover, vital signs, ECG, weight, height, body surface area, complete medical history including FLIPI score, ECOG status, laboratory parameters (including haematological, blood chemistry and urine analysis) lesion assessment as well as the results of pregnancy tests were recorded at various time points during the investigation. Serum levels of rituximab were not measured as part of this study.

The primary objective of the study was to evaluate the benefit of a long-term rituximab maintenance therapy in the target population. The primary efficacy variable was the event-free survival (EFS) defined as time from baseline to progression, relapse, death from any cause, or institution of a new anti-lymphoma treatment. Further, secondary variables such as time to progression (TTP), time to next antilymphoma treatment (TTNLT), duration of response (DR), disease free survival (DFS) and overall survival (OS) were also derived and used during the evaluation of efficacy.

The secondary objective of the study was to describe safety and tolerability profile of a long-term rituximab maintenance therapy. Adverse events (AEs) were continuously recorded throughout the entire study period.

Statistical Analysis

The primary and secondary efficacy parameters were analysed by using Kaplan-Meier product limit method. Survival curves for all endpoints were derived and the mean values were determined by Kaplan-Meier estimation and provided with their 95% confidence intervals. Safety parameters were analysed by using descriptive statistics. *Post-hoc* analysis was conducted in order to determine the probabilities of survival rates (i.e. EFS, OS, TTP, DFS) and to compare of the descriptive statistical parameters (i.e. body weight and vital signs) recorded at the screening visit and at the end of the study.

Results

Overall, 124 patients received at least 1 cycle of rituximab and thus were included in the *intent-to-treat* (ITT) population. All patients received the same dose of rituximab calculated as a function of the body surface area (i.e. 375 mg/m^2), thus individual doses varied between 500 mg and 900 mg. Out of the ITT population, 86 patients received 12 cycles of rituximab, whereas the remaining 38 patients received 1–11 cycles. These non-completer patients were withdrawn from the study population because of the following reasons: lost-to follow up (4), progression of the disease (10), serious adverse event (SAE, 6), consent withdrawal (4), non-compliance (9), unknown reason (1) or because of the decision of the treating physician (3). During the follow-up period, 17 patients were withdrawn prematurely either because of disease progression (8), lost-to follow up (1), consent withdrawal (1), starting new antilymphoma treatment (1) or. In addition, 1 subject during the treatment phase and 6

subjects during the follow-up phase achieved complete remission and thus terminated the study prematurely.

Consequently, 69 patients completed the 36-months follow-up phase. Out of the 124 enrolled subjects, 54 patients were excluded from the *per protocol* (PP) population mainly because of major protocol violation (28 patients) or other reasons also leading to withdrawal from the study (26 patients).

However, out of the 55 prematurely withdrawn patients, 18 patients were included in the PP population though, since these patients had at least one tumour assessment and no major protocol violation (Fig. 1). As a result of rituximab maintenance therapy 7 patients reached complete remission during the course of the study. Progression of the disease was documented in 18 patients out of which 8 patients received 12 cycles of rituximab, whereas the remaining subjects received only 1–10 cycles.

Analysis of the entire ITT population has revealed an estimated mean EFS of 53.9 ± 1.89 months ($CI_{95\%}$: 50.2–57.6 months) (Fig. 2). A somewhat higher mean EFS of 58.9 ± 1.94 months ($CI_{95\%}$: 55.15–62.73 months) was estimated in the PP population (Fig. 3). The post-hoc estimation of the probability of event free survival at 4.3 years was found to be 70.3% ($CI_{95\%}$: 62.5–79.1%).

Similarly to EFS, the mean OS value was slightly higher in the PP population (76.6 ± 0.83 months ($CI_{95\%}$: 75.0–78.3 months) compared to the ITT population (73.0 ± 1.36 months; $CI_{95\%}$: 70.3–75.6 months). Upon this data, the probability of OS at 4 years was found to be 90.7% ($CI_{95\%}$: 85.4–96.4%). High survival rates, however did not allow the estimation of median values for EFS and OS.

Almost identical mean values were estimated for the DFS in the subsets of the ITT ($N = 77$, 66.7 ± 1.50 months, $CI_{95\%}$: 63.8–69.7 months) and PP populations ($N = 45$, 69.7 ± 1.02 months ($CI_{95\%}$: 67.7–71.7 months). In the analysed subset of the ITT population the probability of the DFS at 4 years was found to be 87.9% ($CI_{95\%}$: 80.4–96.2%), whereas in the entire population the probability of the lack of disease progression at 4.3 years was found to be 74.4% (66.7–82.9%).

In the ITT population, the mean TTP (56.0 ± 1.78 months, $CI_{95\%}$: 52.5–59.5 months) was higher than the mean EFS, while in the PP population the mean TTP and EFS values were identical. Likewise, similar mean TTNLT values were estimated in the ITT and in the PP population (59.2 ± 1.49 months ($CI_{95\%}$: 56.3–62.2 months) and 60.8 ± 1.65 months ($CI_{95\%}$: 57.6–64.1 months), respectively). The mean DR was estimated to

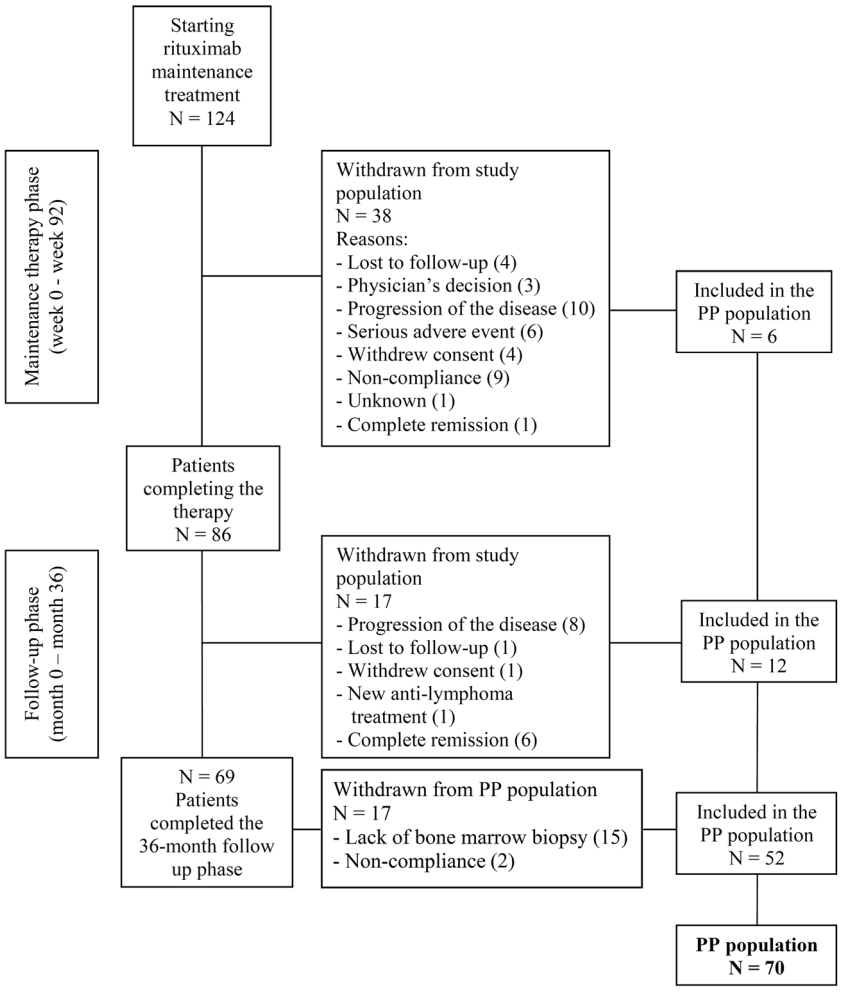

Fig. 1 Disposition of study patients

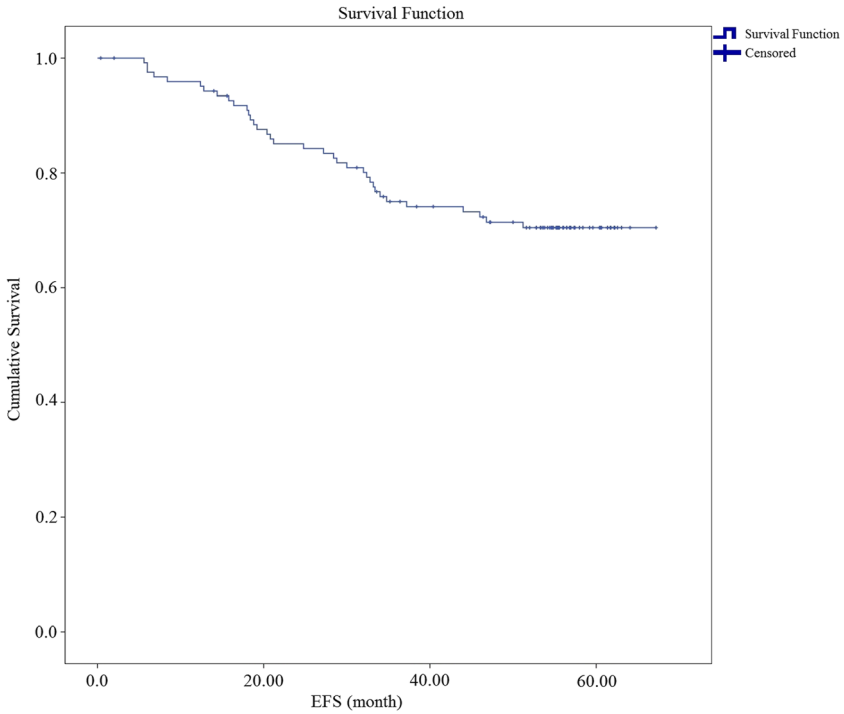

Fig. 2 Kaplan-Meier estimates of event-free survival in the intent-to-treat population ($N = 124$)

be 63.2 ± 1.97 months ($CI_{95\%}$: 59.3–67.0 months) and 66.5 ± 2.05 months ($CI_{95\%}$: 62.5–70.5 months) in the ITT and PP populations, respectively.

There were total 85 AEs (60 non-serious and 25 serious) reported during the study, of which 5 were related and 80 were unrelated to rituximab administration according to the investigators. Out of the 5 related AEs 2 were non-serious (bronchitis and neutropenia) and 3 were serious (granulocytopenia, febrile neutropenia, oral disorder). All SAEs related to rituximab administration were resolved during the course of the study. In 4 patients occurrence secondary malignancies (i.e. neoplasms of the pleura, lung, ovaries and the GI tract) were reported. The most common adverse event affected the respiratory system (i.e. pneumonia). However, the primary disease itself rather than the study medication could be accountable for the occurrence of the reported AEs.

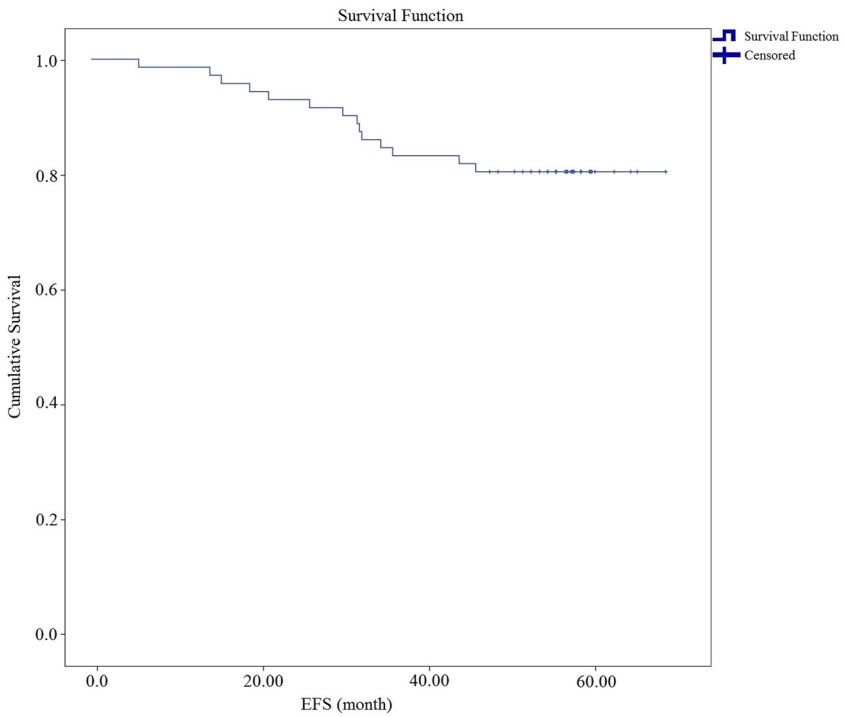

Fig. 3 Kaplan-Meier estimates of event-free survival in the *per protocol* population ($N = 70$)

Overall 13 patients died during the course of the study: 5 patients because of SAEs, whereas 8 patients died as a direct consequence of disease progression.

Body mass and vital signs (i.e. heart rate and blood pressure) recorded at baseline and on the last study visit showed no significant difference ($p > 0.05$). In general, no additional safety data relevant for the therapeutic use of rituximab were identified.

Discussion

Follicular lymphoma is a slowly developing disease which makes the clinical investigations on the efficacy of dedicated therapies rather difficult. The main limitation of this study, however, arises from its single arm design which did not allow for a comparison to either placebo or to active comparator arm. Therefore these results can be appropriately interpreted only in the context of published clinical data provided by randomised trials.

At the time of the initiation of the HUSOM trial in July 2005, evidences were available mostly for the efficacy of prolonged rituximab monotherapy [20–22]. Only the results of the non-randomized ECOG 1496 trial indicated a significant superiority of rituximab maintenance in patients who received previously CVP induction treatment by estimating median TTPs of 4.2 and 1.5 years in the rituximab maintenance and observational arms [23].

Therefore - in parallel with the HUSOM study - two open-label, international, multicentre randomised, phase III trials were initiated in order to demonstrate the efficacy of rituximab maintenance therapy.

The EORTC 20981 was a randomized, open-label, intergroup, multi-center, prospective, controlled clinical trial conducted between November 1998 and April 2004 with 334 patients aiming to compare rituximab maintenance (375 mg/m^2 i.v. every 3 months for up to 24 months) with observation in the treatment of FL patients. In this study the highest median TTP of 51.9 months was estimated in responder patients who received rituximab containing induction treatment (R-CHOP) followed by rituximab maintenance which was significantly higher compared to the results of the three additional arms (median TTP values of 37.5 months for CHOP + maintenance, 22.1 months for R-CHOP + observation and 11.6 months for CHOP + observation regimens; $p < 0.05$ for all comparisons). Irrespective of the response to induction therapy, in the overall study population the median TTP was 42.2 months and 14.3 months in the maintenance and observation arms, respectively ($p < 0.0001$) [24].

The PRIMA trial was undertaken between December 2004, and April 2007, in 223 centres in 25 countries by enrolling 1217 patients with FL who were subjected to rituximab containing induction therapy followed by a 2-year rituximab maintenance monotherapy or observation during this period. The 3-year progression-free survival was found to be 74.9% ($CI_{95\%}$: 70.9–78.9%) in the rituximab maintenance group [25].

Altogether, results of both trials are comparable to the mean TTP (56 months) and 4.3-year probability of lack of disease progression (74.4%) observed in this study.

In light of these, the results of the HUSOM study can be considered as being supportive for the efficacy and safety of 2 years of rituximab maintenance therapy of patients with follicular lymphoma after induction of response with rituximab containing first-line regimen. Maintenance therapy was well tolerated and there were no unexpected safety findings.

The long-term benefit of the maintenance treatment was indicated by the results of the extended follow-up phases of the EORTC 20981 and PRIMA trials both consistently reporting significantly higher progression-free survivals for the active treatment arms at 6 year [26, 27].

In summary, data emerging from controlled clinical trials eventually led to the extension of the approved therapeutic indications of rituximab by the Competent Regulatory Authorities as well as to the inception of maintenance therapy to the routine clinical practice as reflected from the recommendations of relevant therapeutic guidelines [28].

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Compliance with Ethical Standards This study was carried out in accordance with the rules of Good Clinical Practice (GCP) as well as with the basic principles of "Declaration of Helsinki (Fortaleza, 2013)" and was approved by the National Institute of Pharmacy (OGYI, Hungary) and by the Clinical Pharmacology Ethical Committee of the Medical Science Council (ETT-KFEB, Hungary).

Conflict of Interest TS: honoraria, travel reimbursement; AI: advisory role; LS: honoraria; ZG: travel reimbursement; TM: advisory role; JD: advisory role; PD: honoraria; ZB: advisory role; remaining authors have declared no conflicts of interest.

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