INPLASY

Systematic review and meta-analysis of clinical dementia trials with EGb 761 in accordance with the current guideline of the European Medicines Agency

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ADMINISTRATIVE INFORMATION

Support - Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany, sponsored this research and funded its publication.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - MS and MB received honoraria from Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany for scientific consulting. SS is an employee, and RH is a former employee of Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany.

INPLASY registration number: INPLASY202670023

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 9 July 2026 and was last updated on 9 July 2026.

INTRODUCTION

Review question / Objective Question: How does the updated EMA Guideline for the Clinical Investigation of Drugs for Alzheimer's Disease impact on efficacy outcomes of existing clinical trials comparing EGb 761 against placebo in dementia?
A re-analysis of the clinical trials was conducted by applying the concepts of the updated EMA guideline, with the objective to provide a precise and accurate quantification of the therapeutic effects of EGb 761 in patients with dementia.

Rationale Placebo-controlled trials have provided evidence that Ginkgo biloba leaf extract EGb 761 is an effective treatment for dementia. However, most of these studies were completed before the European Medicines Agency (EMA) published its revised guidelines on the Clinical Investigation of Medicines for treating Alzheimer's Disease in 2018. The main change to the previous version of the guideline is the introduction of the estimand framework, which more clearly links the clinical question, trial design, data collection and statistical analysis. A key feature is the explicit choice of strategy for intercurrent events, which occur between randomization and the determination of endpoints. For instance, a patient may stop treatment or take prohibited concomitant medication. Such events may influence the study results. The estimand concept was therefore developed to define how such intercurrent events are handled prospectively in the final statistical analysis. This could involve considering them as part of the treatment effect, incorporating them into a composite endpoint, or using a hypothetical scenario in which they are presumed not to have occurred.
Based on these considerations, existing clinical trials are identified and reanalyzed in accordance with the current version of the EMA guideline.

Condition being studied Alzheimer's dementia, vascular dementia or mixed type. Dementia has a multifactorial etiology, involving neurotoxicity, oxidative damage and neuroinflammation, among other factors.
EGb 761 is a dry extract produced from Ginkgo biloba leaves. Since EGb 761 as herbal preparation contains a variety of bioactive substances, it has the capacity to regulate multiple targets simultaneously. The extract is known to enhance cerebral microcirculation, regulate glycogen synthase kinase-3 beta and modulate protein tau phosphorylation, which results in a reduction of oxidative damage, an inhibition of pro-inflammatory cytokine production, and the promotion of neuroplasticity. EGb 761 is indicated for patients suffering from mild or moderate dementia caused by probable Alzheimer's disease, probable vascular dementia or possible Alzheimer's disease.

METHODS

Search strategy The following terms and their variants were used as search terms: extract of Ginkgo biloba, Ginkgo leaf, dementia, Alzheimer's disease (AD).
No restrictions were placed on the languages of publication or the search period.
The following databases and strategies were included:
MEDLINE via the Pubmed interface:
#1 MeSH Term: Dementia OR
#2 Title/Abstract: Dementia AND
#3 Title/Abstract: ("ginkgo biloba" OR "ginkgo biloba 761" OR "ginkgo biloba egb" OR "ginkgo biloba egb 761" OR "ginkgo biloba extract egb 761" OR "ginkgo biloba extract gbe" OR "gingko biloba extract" OR "gingko biloba extract egb" OR "gingko biloba extract egb 761" OR "maidenhair extract" OR "maidenhair tree" OR "egb 761" OR "gbe 761"OR tebonin OR tanakan OR "rokan" OR "ginkoba") AND
#4 Article type: randomized controlled trial
EmBase:
L1 Broad search: 'dementia'/exp OR 'dementia' OR 'alzheimer disease'/exp OR 'alzheimer disease' ;
L2 Title abstract: "((ginkgo biloba) OR (ginkgo biloba extract) OR (ginkgo biloba extract GBE) OR (ginkgo biloba 761) OR (ginkgo biloba EGB) OR (ginkgo biloba EGB 761) OR (ginkgo biloba extract EGB 761) OR (EGB 761) OR (maidenhair extract) OR (maidenhair tree) OR (GBE 761) OR tebonin OR tanakan OR rokan OR ginkoba) AND
L3 Study types: ((controlled clinical trial) OR (randomized controlled trial))
L4 Source: [embase]/lim NOT ([embase]/lim AND [medline]/lim).

Participant or population Patients treated in an outpatient setting and suffering from mild or moderate dementia caused by probable Alzheimer's disease, probable vascular dementia or possible Alzheimer's disease in accordance with internationally recognized criteria, i.e. DSM-III-R (American Psychiatric Association, 1987), NINCDS-ADRDA (McKhann et al., 1984) or NINDS-AIREN (Roman et al., 1993).

Intervention Daily dosage of 240 mg of EGb 761 for 24 (± 2) weeks.

Comparator Placebo.

Study designs to be included Randomised placebo controlled double blind trials on EGb 761 at a daily dosage of 240 mg over 24 (± 2) weeks.

Eligibility criteria Exclusion:
Studies not conforming to characteristics set out in section 15
Publications such as non systematic reviews, editorials, conference abstracts, case reports, opinion pieces, editorials, comments, news, letters.

Information sources Results from electronic database searches (Pubmed, EmBase)
References cited in Cochrane review on Ginkgo in dementia (Wieland LS, Ludeman E, Chi Y, Feinberg TM, Chen I-H, Chen K-H, Zhu Y, Wolverson E, Amri H. Ginkgo biloba for cognitive impairment and dementia. Cochrane Database of Systematic Reviews 2026, Issue 2. Art. No.: CD013661. DOI: 10.1002/14651858.CD013661.pub2.Wieland et al., 2026)
Search in the registry clinicaltrials.gov
References provided by authors.

Main outcome(s) The following outcomes were defined: Cognition, Global clinical assessment, Activities of daily living, responder analysis
According to the EMA guideline the primary domains for outcome assessment are cognition, activities of daily living (ADL) and global clinical status. Therefore, these endpoints are chosen for reanalysis of single trials identified during the search. Results from these endpoints were pooled and used for the meta-analysis.
A composite response criterion was established to measure clinically significant improvement in cognitive function without deterioration in functional or global domains and without premature termination of randomized treatment or

administration of prohibited concomitant medication.
For cognitive function, an improvement of at least 4 points on the ADAS-cog scale or 3 points on the SKT total score was considered clinically significant. A longitudinal analysis showed that the total scores on both scales are highly correlated. An improvement of 3 points on the SKT is equivalent to an improvement of 4 points on the ADAS-cog scale.

Data management The systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Two reviewers (both knowledgeable on the review topic and on methodology matters) independently reviewed the titles and abstracts and excluded irrelevant records. Any disagreement was resolved by third reviewer. Decisions on eligibility of full text articles were recorded in MS Word tables and summarized in the PRISMA flow chart. Then, the full text screening of the remaining records was conducted.
Data extraction from the selected full text articles was not performed, as all data were available in the internal database of the study sponsor. A statistical analysis plan was defined in advance. This outlined the data management procedures, i.e. which datasets would be analysed and how. In accordance with the SAP, single trials were analysed in the study sponsor's integrated database.
Analysis of single trials: Based on imputed data of from each individual trial, ANOVA / ANCOVA models including the same factors and covariates as in the original analysis of in the individual trials were applied. Overall inference for individual the single trials was obtained by applying Rubin's rules on the estimates obtained from every imputed/ completed data set (see Ratitch and O'Kelly, 2011). Results per single trials were calculated using SAS 9.4.
After this step, the meta-analysis was carried out in accordance with the current EMA guideline, using pooled data from the main outcomes of cognition, activities of daily living and global clinical impression. Treatment response was defined as a clinically relevant improvement in cognition, with no deterioration in activities of daily living or global clinical judgement, and no premature discontinuation of treatment or intake of prohibited medication.
Meta-analysis: In the meta-analysis, the trial specific results were combined using R (package meta, function metacont for continuous outcomes and metabin for binary outcomes) and presented as forest plots (package meta, function forest). Inverse variance weighting was applied for combining the results of the individual trials using random effects models. Standardized mean differences with 95% confidence intervals were calculated for continuous endpoints. For binary endpoints odds ratios with 95% confidence intervals were used as effect measures. Heterogeneity was quantified by calculating the I2 statistics. The importance of the observed I2 depends on the magnitude and direction of effects. If I2 was larger than 50%, a sensitivity analysis was performed by removing single trials from the analysis.

Quality assessment / Risk of bias analysis The risk of bias assessment for individual trials was conducted using the Cochrane RoB 2 tool (Higgins, 2011 #8342).
All studies were conducted in accordance with GCP guidelines and originally published in peer-reviewed journals. The results indicated adequate random sequence generation, allocation concealment and blinding of participants and personnel. However, blinding of the outcome assessment was unclear in two studies, and the risk of selection bias (reporting bias) was unclear in all of them. Overall, the quality of the included trials was good, with a low risk of bias.
For assessment of systematic literature reviews, the PRISMA 2020 and AMSTAR-2 checklists were used.
The limitations of this re-analysis lie in its retrospective nature, which may introduce bias. While the overall risk of bias is low, the risk of a selection bias is unclear, given that the re-analysed studies were neither published nor preregistered. Furthermore, five out of six of the included studies were sponsored by the manufacturer of EGb 761, which is another potential source of bias. These factors must be kept in mind when interpreting the results of the present meta-analysis. Nevertheless, re-analyzing existing datasets derived from GCP-adherent studies after the change in guidelines allows the question of efficacy to be addressed without the need to repeat clinical studies.

Strategy of data synthesis Two reviewers independently reviewed the titles and abstracts and excluded irrelevant records. Then, the full text of the remaining records was studied. The selected randomized controlled trials had to be conducted in accordance with Good Clinical Practice (GCP) guidelines, comparing EGb 761 with placebo to included into the meta-analysis calculation.
The re-analysis of the selected placebo-controlled clinical trials investigating the efficacy of 240 mg EGb 761 daily in patients with dementia (Alzheimer's dementia, vascular dementia or mixed

type) was performed in consideration of main aspects of the current version of the EMA guideline on the clinical investigation of medicines for the treatment of Alzheimer's disease (Committee for Medicinal Products for Human Use, 2018). Based on imputed data of from each individual trial, ANOVA / ANCOVA models including the same factors and covariates as in the original analysis of in the individual trials were applied. Overall inference for individual trials was obtained by applying Rubin's rules on the estimates obtained from every imputed/ completed data set (Ratitch and O'Kelly, 2011).
In a second step, a meta-analysis of the trials based on the results of the re-analyzed single trials was conducted. The results for all three main outcomes were essentially like those of a meta-analysis based on the original results of the same studies.
Trial specific results were combined using R (package meta, function metacont for continuous outcomes and metabin for binary outcomes) and presented as forest plots (package meta, function forest). Inverse variance weighting was applied for combining the results of the individual trials using random effects models. Standardized mean differences with 95% confidence intervals were calculated for continuous endpoints. For binary endpoints odds ratios with 95% confidence intervals were used as effect measures.

Subgroup analysis Subgroup analysis was not performed.

Sensitivity analysis Heterogeneity was quantified by calculating the I2 statistics. The importance of the observed I2 depends on the magnitude and direction of effects. If I2 was larger than 50%, a sensitivity analysis was performed by removing single trials from the analysis.

Language restriction No language restrictions.

Country(ies) involved Germany, Spain.

Other relevant information The SLR was carried out in May and June 2026.
At this stage, a signed statistical analysis plan as well as the protocol were available.
The protocol was inadvertently not submitted.

Keywords Ginkgo biloba leaf extract; EGb 761; clinical trials; reanalysis, dementia; estimands; cognition.

Dissemination plans Original publication in an international, peer-reviewed, open access journal in English.

Contributions of each author

Author 1 - Mark Stemmler - Author 1 interpreted the data, revised and edited the manuscript and carried out a critical review.
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