

# Effects of galantamine and galantamine combined with nimodipine on cognitive speed and quality of life in mixed dementia: a 24-week, randomized, placebo-controlled exploratory trial (the REMIX study)

Efeitos da galantamina e da galantamina combinada à nimodipina sobre a velocidade de processamento cognitivo e qualidade de vida na demência mista: ensaio clínico exploratório, randomizado e controlado com placebo (estudo REMIX)

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## ABSTRACT

The effects of galantamine (GAL) on quality of life (QoL) and cognitive speed, as well its effects combined with nimodipine (NIM) in Alzheimer disease (AD) with cerebrovascular disease (mixed dementia), have not been explored. **Method:** Double-blind, placebo-controlled, multicenter Brazilian trial, studying the effects of GAL/NIM vs. GAL/placebo (PLA) in mild to moderate mixed dementia. Patients were randomized to receive GAL/NIM or GAL/PLA for 24 weeks. Primary efficacy measures were changes on a computerized neuropsychological battery (CNTB) and QoL Scale in Alzheimer's Disease (QoL-AD) from baseline to week 24. **Results:** Twenty-one patients received at least one drug dose (9 GAL/NIM and 12 GAL/PLA). Groups were matched for age, sex, education, cognitive and QoL scores at baseline. No significant differences were observed between groups on primary or secondary measures. QoL and cognitive performance showed significant improvement ( $p < 0.05$ ) from baseline when all GAL-treated patients were analyzed. Adverse events were predominantly mild to moderate. **Conclusion:** GAL treatment improved QoL in mixed dementia, in addition to its previously known cognitive benefits. The combination GAL/NIM was not advantageous. However, the small sample size precludes any definitive conclusions. Trial registered at ClinicalTrials.gov: NCT00814658

**Keywords:** Alzheimer disease, cerebrovascular disorders, galantamine, nimodipine.

## RESUMO

Os efeitos da galantamina (GAL) sobre qualidade de vida (QdV) e velocidade de processamento cognitivo, bem como da combinação com nimodipina (NIM) no tratamento da doença de Alzheimer (DA) com doença cerebrovascular (demência mista) ainda não foram investigados. **Método:** Estudo multicêntrico brasileiro, duplo-cego, controlado com placebo, avaliando os efeitos de GAL/NIM x GAL/placebo (PLA) na demência mista leve a moderada. Pacientes receberam tratamento com GAL/NIM ou GAL/PLA por 24 semanas. Medidas de eficácia primária foram as variações no desempenho em bateria de testes neuropsicológicos computadorizados e na escala QdV-DA ao final do

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**Conflict of interest:** This study and the present communication were supported by Janssen-Cilag Farmacêutica Ltda., São Paulo, Brazil.

estudo. **Resultados:** Vinte um pacientes receberam pelo menos uma dose da droga (9 GAL/NIM e 12 GAL/PLA). Os grupos foram emparelhados por idade, sexo, escolaridade, escores cognitivos e de QdV na linha de base. Não foram observadas diferenças significativas entre os dois grupos nas medidas de eficácia primária e secundária. Na avaliação de todos os pacientes que receberam GAL, houve melhora significativa ( $p < 0,05$ ) em QdV-DA e desempenho cognitivo. Os eventos adversos foram predominantemente leves a moderados. **Conclusão:** O tratamento com GAL proporcionou melhora da QdV na demência mista, além dos benefícios cognitivos previamente conhecidos. A combinação GAL/NIM não foi vantajosa. O reduzido tamanho amostral impede conclusões definitivas.

**Palavras-chave:** doença de Alzheimer, desordens cerebrovasculares, galantamina, nimodipina.

Mixed dementia (defined as an association of both Alzheimer disease – AD – and cerebrovascular disease – CVD) is a common cause of dementia worldwide<sup>1</sup>. It is usually underdiagnosed and, according to a Brazilian study, mixed dementia is the second most frequent cause of dementia among people aged  $\geq 65$  years in the country, being responsible for circa 14% of all cases<sup>2</sup>.

There is still a lack of well-established therapeutic options for patients with this condition based on high quality evidence. Most studies have investigated the efficacy and safety of different agents on each condition separately (AD or CVD)<sup>3,4,5</sup>, even though the association of AD and CVD is well documented in the medical literature<sup>6</sup>.

Ischemic lesions seem to play a prominent role in cognitive decline, even in the presence of AD pathology. Cholinesterase inhibitors (ChEIs), especially galantamine (GAL), proved to be effective in the treatment of AD<sup>5</sup> and also in the treatment of patients with mixed dementia (AD with CVD)<sup>7</sup>. In a study with rivastigmine, patients with AD and concurrent vascular risk factors had more benefits on cognition and functional performance than patients without concurrent vascular risk factors<sup>8</sup>.

GAL has demonstrated beneficial effects on both cognitive and non-cognitive outcomes in patients with VaD and in AD with CVD<sup>9,10</sup>. GAL is the only ChEI approved for treatment of patients with AD with CVD in Brazil and in some other countries. However, its effects on quality of life (QoL) and cognitive speed in patients with mixed dementia have not been investigated so far. Moreover, the efficacy of GAL treatment combined with nimodipine (NIM), a calcium channel antagonist with putative neuroprotective effects in patients with subcortical vascular dementia, has not been explored. NIM improves cerebral blood flow via its vasodilatory effects, and, by restricting the influx of calcium ions into neurons, may prevent neuronal apoptosis<sup>11</sup>. A few studies have found evidence that NIM provides some short-term benefits, mainly in measures of cognitive function and global impression<sup>3</sup>.

The aim of the present exploratory study was to compare GAL plus NIM vs. GAL alone on cognitive speed and QoL measures in patients with mixed dementia.

## METHOD

### Study design

This was a double-blind, placebo-controlled, exploratory, parallel study involving 11 centers in four Brazilian states (Minas Gerais, Rio de Janeiro, Rio Grande do Sul, and São Paulo), conducted from May, 2008 to October, 2009. Patients were randomized (1:1) to one of two treatment arms: GAL (16-24 mg/day) plus NIM (90 mg/day) or GAL (16-24 mg/day) plus placebo (PLA). Both groups were followed for 24 weeks. GAL dose was started at 8 mg QD, with monthly increments up to 24 mg QD if well-tolerated, for both arms. NIM dose was 30 mg three times a day (TID) throughout the study and PLA was also given TID. Patients were submitted to six clinical evaluations throughout the study: enrollment visit, baseline, and follow-up visits at 4, 8, 16 and 24 weeks after baseline.

The simple random allocation sequence was performed using the PLAN procedure of SAS software, Version 9.1.3 (SAS Institute Inc., Cary, NC, USA). Each patient, at the enrollment, received a randomization number and the corresponding numbered medication. To ensure the blinding was maintained (for both patients and study team), the medication was provided into recipients as tablets (8mg, 16mg, 24mg of GAL and 30mg of NIM or PLA) that were similar in size and appearance. The study was performed under the Good Clinical Practice regulations and according to the Declaration of Helsinki. The protocol and the informed consent for patients and caregivers were approved by the Institutional Review Board of each site. Written informed consent from patients and their responsible relatives was required prior to enrollment.

The key co-primary efficacy measures were change from baseline to week 24 in cognitive speed and on QoL. The secondary endpoints were: (1) global cognitive performance; (2) global clinical impression; and (3) neuropsychiatric symptoms. Two separate analyses were performed considering the pilot study nature of this trial: between treatment

groups' comparison (GAL/NIM vs. GAL/PLA) and changes in efficacy measures from baseline to end of follow-up (within group comparison).

### Study patients

Patients were eligible to be included in the trial if they met the following criteria: (1) men or women outpatients; (2) age  $\geq 65$  years; (3) fulfilling DSM-IV diagnostic criteria for dementia<sup>12</sup>; (4) fulfilling NINDS-AIREN diagnostic criteria for AD with CVD (mixed dementia)<sup>13</sup>; (5) mild to moderate dementia, with Mini-Mental State Examination (MMSE)<sup>14</sup> scores ranging from 10 to 26, inclusive; (6) presence of a caregiver; (7) signed informed consent provided by patients and/or their legally-accepted representatives. Patients had to present significant CVD on magnetic resonance imaging, namely the presence of cortical lesions and/or subcortical lesions (periventricular and deep white matter changes) affecting at least 25% of the subcortical area.

The following exclusion criteria were adopted: (1) illiteracy; (2) any other neurodegenerative disorder, such as Parkinson's disease, frontotemporal dementia, Huntington's disease, Down syndrome, or Creutzfeldt-Jakob disease; (3) current or past (last six months) clinical history of hepatic or renal failure, history of significant cardiac, pulmonary, gastrointestinal, endocrine, metabolic, neurologic or psychiatric disturbances; or of urinary flow obstruction; (4) cognitive impairment resulting from acute cerebral trauma, hypoxic cerebral damage, vitamin deficiency states, infections, primary or metastatic brain tumor, endocrine or metabolic disease, mental retardation or oligophrenia; (5) use of benzodiazepines or antiepileptic drugs in the last three months; (6) use of any experimental treatment (for dementia or any other condition) in the last 12 months; (7) history of drug or alcohol abuse; (8) participation in previous studies with GAL; and (9) history of known allergy or hypersensitivity to ChEIs. Patients who had taken ChEIs or memantine in the past could participate in the trial if the drug was discontinued at least 30 days before the first evaluation.

### Outcome measures

Primary efficacy measures were performed using a computerized neuropsychological battery (CNTB)<sup>15,16</sup> and the scores on a QoL measure (the QoL Scale in Alzheimer's Disease, QoL-AD)<sup>17,18</sup> at the end of the 24<sup>th</sup> week of treatment. The CNTB included tasks assessing attention and memory (simple and double-choice reaction tasks, face recognition and word-list learning tasks) assessed as reaction times expressed in milliseconds. QoL-AD includes three versions: two caregiver's versions (about patients' and their own perceived QoL) and a patient's version. The scale is composed of 13 items that measure the domains of physical

condition, mood, memory, functional abilities, interpersonal relationships, ability to participate in meaningful activities, financial situation, and global assessments of self as a whole and QoL as a whole. Each item is assessed on a 4-point scale (1=poor, 4= excellent). Scale scores range from 13 to 52, with higher scores indicating greater QoL.

Secondary efficacy measures were: Alzheimer's disease Assessment Scale-Cognitive Subscale (ADAS-Cog)<sup>19,20</sup>, Clinician Global Impression Improvement Scale (CGI-I)<sup>21</sup>, Neuropsychiatric Inventory (NPI)<sup>22,23</sup> and Mini-Mental State Examination (MMSE)<sup>14,24</sup>. Tolerability was assessed based on the rate and severity of investigator-recorded adverse events.

### Statistical analysis

The intention-to-treat population for efficacy and safety included all patients who received at least one dose of the study medication and had at least one safety evaluation after the first visit. An exploratory approach was adopted since similar studies with both drugs and assessing the same outcomes were not available to our knowledge. Thus, expected effect size to use in sample size calculation could not be obtained from the literature and the investigators assumed that 40 patients enrolled in each arm should be sufficient to derive robust estimations of clinical benefit in this pilot study. Efficacy was analyzed as the difference in mean change from baseline to endpoint between treatment groups and within groups for the CNTB, QoL-AD, ADAS-Cog, CGI-I, NPI, and MMSE scores. Repeated Measures Analyses of Variance were employed to both between-group and within-group comparisons. All statistical tests assumed a 5% level of significance.

## RESULTS

Twenty-one patients were enrolled and randomized and received at least one dose of the proposed drug regimen: 9 in the GAL/NIM group and 12 in the GAL/PLA group. The study did not reach the expected sample size mainly due to the strict eligibility criteria established to ensure that only mixed dementia patients would be enrolled. No differences between the two groups were observed in terms of age ( $p=0.172$ ), gender distribution ( $p=0.331$ ) and educational level ( $p=0.464$ ) (Table 1). Baseline MMSE scores, CNTB measures, QoL, ADAS-Cog and NPI scores were also similar between the two groups (Table 2). Five patients (55.6%) in the GAL/NIM and 8 (66.7%) in the GAL/PLA group completed the study. Reasons for dropout were: 4 due to adverse events (in visit 3); 2 due to adverse event and 1 medical criteria (in visit 4); 1 due to lost to follow up (visit 6) (Figure 1).

**Table 1.** Baseline sociodemographic and clinical characteristics of the study participants.

Variable (mean±SD)	GAL/NIM (n=9)	GAL/PLA (n=12)	Total sample	p-value
Age	78.1±5.3	74.3±6.5	76.0±6.2	0.172
Sex	5F:4M	10F:2M	15F:6M	0.331
Years of education	5.0±3.3	4.0±2.7	4.4±2.9	0.464
Disease duration (months)	29.8±33.0	5.6±10.8	14.5±24.1	0.0078
Subcortical vascular disease - n (%)	8 (88.9%)	12 (100%)	20 (95.2%)	0.429
MMSE	15.4±5.6	17.9±3.8	16.9±4.7	0.243

GAL: galantamine; NIM: nimodipine; PLA: placebo; SD: standard deviation; MMSE: Mini-Mental State Exam.

**Table 2.** Results for the computerized neuropsychological battery test components, reaction times (milliseconds).

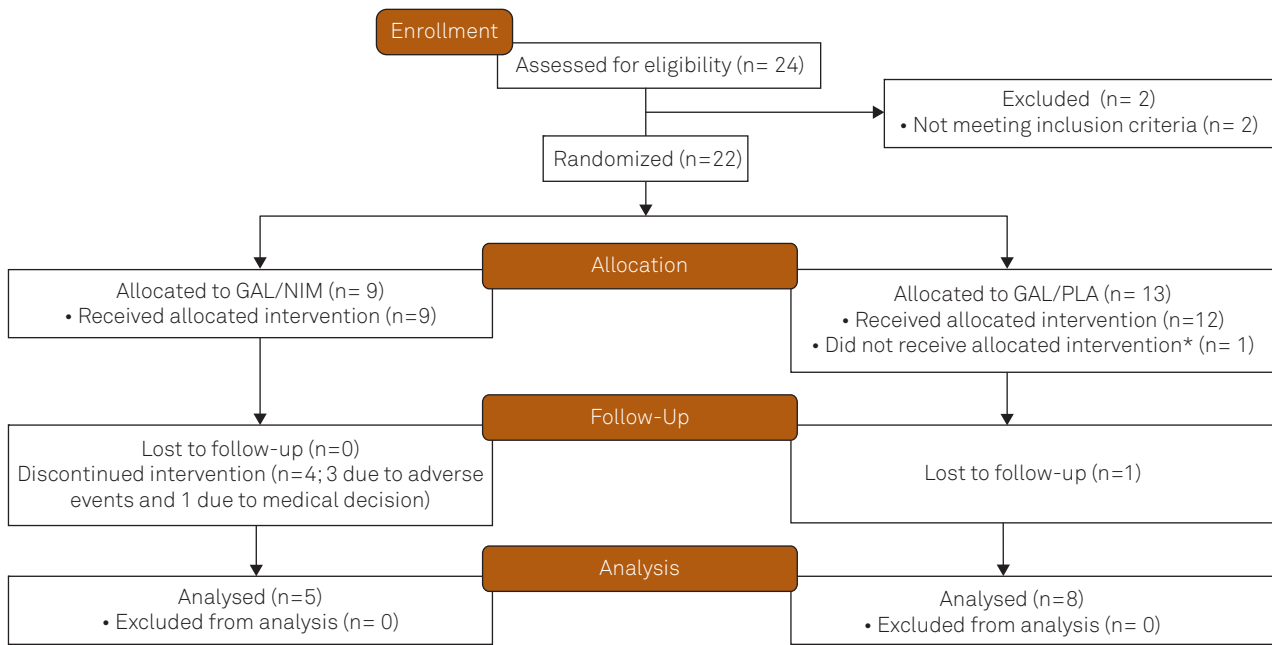
Outcome measure		GAL/NIM	GAL/PLA	Total sample	p-value
Simple-choice reaction time Test (n=12)	Baseline	1,208.7±1,670.0	646.7±314.8	880.9±1,073.3	0.337*
	24-weeks	467.6±336.7	618.7±329.8	555.7±326.5	
	Within-group change			-325.2	
Two-choice reaction time Test (n=12)	Baseline	1,785.5±1,793.7	1,279.5±696.7	1,490.3±1,225.8	0.274*
	24-weeks	727.6±375.0	1,197.9±528.3	1,001.9±511.9	
	Within-group change			-488.4	
Face Recognition Test (n=11)	Baseline	2,890.2±1,432.1	3,168.8±943.0	3,067.5±1,081.0	0.256*
	24-weeks	1,730.7±1,514.1	3,148.1±1,964.3	2,632.7±1,874.6	
	Within-group change			-434.8	
Word Recognition and Learning Test (n=12)	Baseline	2,166.1±715.4	3,387.3±2,214.0	2,878.4±1,804.2	0.859*
	24-weeks	1,722.0±1,174.2	3,104.6±1,328.3	2,528.5±1,403.8	
	Within-group change			-349.9	

GAL: galantamine; NIM: nimodipine; PLA: placebo; \*p-value: estimated using two-factors repeated measure ANOVA (treatment group and visit); \*\*p-value: estimated using single-factor repeated measure ANOVA (visit).

### Efficacy

For the between-group comparison (GAL/NIM vs. GAL/PLA), no significant differences on primary efficacy measure were found on the CNTB (Table 2) and QoL-AD (Table 3). The secondary efficacy endpoint findings were also similar

between GAL/NIM and GAL/PLA, with no statistical significance in between-group comparisons for the ADAS-Cog, CGI-I, MMSE or NPI, suggesting that adjunctive NIM did not contribute to additional benefits (Table 4). Thus, further analyses were developed for efficacy measures using the



\*One patient changed treatment arm for a short period during the study and was excluded from the analysis.

Figure. CONSORT 2010 Study Flow Diagram.

Table 3. Results for the QoL-AD questionnaire, total scores.

Outcome measure		GAL/NIM	GAL/PLA	Total sample	p-value
Caregiver (n=12)	Baseline	35.2±9.3	36.0±9.2	35.6±8.8	0.459*
	24-weeks	36.6±4.6	34.3±7.2	35.2±6.1	
	Within-group change			-0.4	
Patient as assessed by caregiver (n=12)	Baseline	28.4±10.7	29.7±10.1	29.2±9.9	0.618*
	24-weeks	29.8±5.7	28.4±7.2	29.0±6.4	
	Within-group change			-0.2	
Patient (n=11)	Baseline	31.6±6.9	28.3±5.6	29.8±6.2	0.965*
	24-weeks	36.6±6.2	33.2±5.4	34.7±5.8	
	Within-group change			4.9	

QoL-AD: QOL Scale in Alzheimer's disease; GAL: galantamine; NIM: nimodipine; PLA: placebo; \*p-value: estimated using two-factors repeated measure ANOVA (treatment group and visit); \*\*p-value: estimated using single-factor repeated measure ANOVA (visit).

total sample (both GAL/NIM and GAL/PLA patients), assessing if 24-week therapy with GAL produces significant improvements in cognitive speed, QoL and other dementia clinically-relevant measures.

The patient component of the QoL-AD measure (patients' self-reported QoL) showed significant improvements from baseline to week 24 (difference of means=4.9; p=0.027) when all GAL treated patients were combined in the analysis (regardless initial treatment arm). CNTB individual tests and caregivers versions of the QoL-AD questionnaire did not present significant differences between baseline and the end of follow-up (Tables 2 and 3). Regarding the secondary efficacy measures, GAL treatment led to significant improvements in ADAS-Cog (difference of mean=-3.9; p=0.029) and MMSE (1.2; p=0.037) at 24 weeks as compared to baseline values. Significant changes were not observed for CGI-I and NPI (Table 4).

### Adverse events

Six patients discontinued the treatment due to adverse events (three in each group), five mostly because of nausea,

vomiting and diarrhea, which were predominantly mild to moderate, and one due to respiratory distress (in the GAL/PLA arm), rated as severe by the investigator.

### DISCUSSION

This is the first randomized, double-blind, multicenter clinical trial designed to prospectively evaluate the efficacy and safety of the association between a ChEI and NIM in patients with mixed dementia. The findings of our study showed significant improvement in both QoL-AD, ADAS-Cog and MMSE scores at week 24, compared with baseline, among GAL treated patients (regardless the association with NIM), despite its small sample size. The association of NIM to GAL did not lead to any clinical advantage. We believe that these results may be relevant for current clinical practice and also for future research.

GAL has been tested in several randomized clinical trials for AD<sup>3,16,25,26</sup> and has been also evaluated in a systematic review, which examined its efficacy and safety for patients

Table 4. Results for the secondary efficacy measures.

Outcome measure		GAL/NIM	GAL/PLA	Total sample	p-value
ADAS-Cog (n=11)	Baseline	26.4±11.2	30.7±11.8	28.7±11.2	0.135*
	24-weeks	25.0±9.7	24.6±12.1	24.8±10.5	
	Within-group change			-3.9	
CGI-I at 24 weeks (n=12)	Very much improved	0 (0%)	0 (0%)	0 (0%)	1.000*
	Much improved	1 (20%)	2 (25%)	3 (23.1%)	
	Minimally improved	3 (60%)	4 (50%)	7 (53.8%)	
	No change	1 (20%)	1 (12.5%)	2 (15.4%)	
	Minimally worse	0 (0%)	0 (0%)	0 (0%)	
	Much worse	0 (0%)	0 (0%)	0 (0%)	
NPI (n=12)	Baseline	23.4±8.1	27.7±17.9	25.9±14.3	0.765*
	24-weeks	15±11.5	21.7±16.9	18.9±14.7	
	Within-group change			-7.0	
MMSE (n=12)	Baseline	15.4±3.8	16.6±2.6	16.1±3.1	0.187*
	24-weeks	17.6±5.3	17.1±3.7	17.3±4.2	
	Within-group change			1.2	

ADAS-Cog: Alzheimer's disease Assessment Scale-Cognitive Subscale; CGI-I: Clinician Global Impression Improvement Scale; NPI: Neuropsychiatric Inventory; MMSE: Mini-Mental State Examination; GAL: galantamine; NIM: nimodipine; PLA: placebo; \*p-value: estimated using two-factors repeated measure ANOVA (treatment group and visit); \*\*p-value: estimated using single-factor repeated measure ANOVA (visit).



with vascular cognitive impairment, but also included studies enrolling mixed dementia patients<sup>4</sup>. Two studies were deemed eligible for the systematic review (GAL-INT-26 and GAL-INT-6), the first assessing a population with probable vascular dementia<sup>27</sup> and the other, a mixed population of vascular dementia and AD with simultaneous CVD patients<sup>9,28</sup>.

In GAL-INT-6 study, patients with vascular dementia and AD with CVD showed greater clinical benefit over placebo on ADAS-Cog, clinician's interview-based impression of change plus caregiver input (CIBIC-plus), activities of daily living and on behavioral symptoms measures<sup>9</sup>. The GAL-INT-6 study observed similar benefits on ADAS-Cog among vascular dementia patients, but was not able to verify improvements in other efficacy measures. The GAL-INT-26 trial showed that GAL was superior to placebo for three of the four subtypes of VaD studied (multiple lacunar infarcts, extensive white matter disease and multiple territorial infarcts) in ADAS-cog improvement<sup>27</sup>. Interestingly, in our study most of the mixed dementia patients had subcortical vascular disease. These and other studies<sup>4,7,9,27,28</sup> reported higher rates of nausea and vomiting in GAL treated participants, compared with placebo, consistent with our results and the generally favorable safety profile observed in previous studies in AD disease<sup>5,25,26,29</sup>.

A systematic review<sup>3</sup> of 15 trials evaluating the efficacy of NIM in AD, CVD and mixed dementia found benefits of the NIM therapy on short-term outcomes of global and cognitive function, when results were pooled together, despite dementia specific etiology. Separate analysis of AD and CVD patients showed similar results. Given its mechanism of action, we hypothesized that co-administration with GAL could improve clinical outcomes in comparison to

GAL monotherapy in these patients. However, our results did not show any additional efficacy benefits of the association therapy.

The major limitation of our study was the small sample size. This was probably due to the short enrollment period and to the rigorous inclusion criteria that were adopted. The latter aimed to ensure the inclusion of patients truly presenting mixed dementia. An additional limitation is the somewhat large dropout rate, which may be explained by the clinical profile of the population, with several patients presenting comorbidities that impact tolerability and adherence to treatment.

In conclusion, in this exploratory, randomized, 24-week, placebo-controlled trial, GAL was well-tolerated and efficacious in improving QoL in patients with mixed dementia, in addition to its already known cognitive benefits. The combination of GAL to NIM did not demonstrate any apparent advantage, although this aspect should be further explored in larger studies.

## Acknowledgments

We thank the investigators Irismar Reis and Vitor Tumas, the patients and their relatives for their participation in the study.

We thank the following colleagues, who contributed to data collection in the different participating centers: Cloyra Almeida, Etelvina Lucas dos Santos, Henrique Cerqueira Guimarães, Irene Moreira, Gilberto Alves, Margarete Borges, Patrícia Paes Araújo Fialho, Rogério Gomes Beato, Viviane Amaral Carvalho.

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