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Featured Article

The effects of DL-3-n-butylphthalide in patients with vascular cognitive impairment no dementia caused by subcortical ischemic small vessel disease: A multicentre, randomized, double-blind, placebo-controlled trial

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Abstract

Background: Vascular cognitive impairment no dementia (VCIND) is very common among the aged and tends to progress to dementia, but there have been no proper large-scale intervention trials dedicated to it. VCIND caused by subcortical ischemic small vessel disease (hereinafter, subcortical VCIND) represents a relatively homogeneous disease process and is a suitable target for therapeutic trials investigating VCIND. Preclinical trials showed that dl-3-n-butylphthalide (NBP) is effective for cognitive impairment of vascular origin.

Methods: In this randomized, double-blind, placebo-controlled trial, we enrolled patients aged 50–70 years who had a diagnosis of subcortical VCIND at 15 academic medical centers in China. Inclusion criteria included a clinical dementia rating $\geq$0.5 on at least one domain and global score $\leq$0.5; a mini-mental state examination score $\geq$20 (primary school) or $\geq$24 (junior school or above); and brain magnetic resonance imaging consistent with subcortical ischemic small vessel disease. Patients were randomly assigned to NBP 200 mg three times daily or matched placebo (1:1) for 24 weeks according to a computer-generated randomization protocol. All patients and study personnel were masked to treatment assignment. Primary outcome measures were the changes in Alzheimer's disease assessment scale-cognitive subscale (ADAS-cog) and clinician's interview-based impression of change plus caregiver input (CIBIC-plus) after 24 weeks. All patients were

The authors declare that they have no conflicts of interest.

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monitored for adverse events (AEs). Outcome measures were analyzed for both the intention-to-treat (ITT) population and the per protocol population.

Results: This study enrolled 281 patients. NBP showed greater effects than placebo on ADAS-cog (NBP change −2.46 vs. placebo −1.39; $P = .03$; ITT) and CIBIC-plus (80 [57.1%] vs. 59 [42.1%] patients improved; $P = .01$; ITT). NBP-related AE were uncommon and primarily consisted of mild gastrointestinal symptoms.

Conclusions: Over the 6-month treatment period, NBP was effective for improving cognitive and global functioning in patients with subcortical VCIND and exhibited good safety.

Keywords: DL-3-n-Butylphthalide; Vascular cognitive impairment no dementia; Cerebral small vessel disease; Randomized controlled trial; Multicentre study

1. Introduction

Vascular cognitive impairment no dementia (VCIND) refers to cognitive disorders that arise from underlying vascular causes in patients who do not meet the criteria for vascular dementia (VaD) [1,2]. It is a very common form of cognitive impairment among the aged globally. The Canadian Study of Health and Aging (CSHA) reported that VCIND was the most prevalent form of vascular cognitive impairment among those aged 65–84 years, with an estimated prevalence of 2.6% [3,4]. The American Aging, Demographics, and Memory Study reported that the prevalence of VCIND among those aged ≥71 years was 5.7%, accounting for 25.6% of the total cases, second only to the prodromal AD subtype (34.2%) [5]. With a high prevalence of cerebral vascular disease in China, VCIND might be relatively more common. The China Cognition and Aging Study found that VCIND is the most common subtype of mild cognitive impairment (MCI) in China, accounting for 42.0% of the total cases. The prevalence of VCIND is 8.7% among Chinese people over the age of 65 years, overwhelming that of amnestic MCI (6.1%) [6]. Patients with VCIND are at high risk for developing dementia. The CSHA study found that 50% of those patients with VCIND progressed to dementia over 5 years of follow-up, and the rate of institutionalization and mortality among individuals with VCIND is similar to that of those with VaD [1,3]. These results emphasize the importance of VCIND and call for more attention and greater effort toward addressing this relatively neglected patient population. Early intervention of VCIND holds the potential to delay or even reverse the cognitive deterioration, and from a public health viewpoint, may lead to a global decrease of incident dementia. However, there has been no effective treatment specifically for VCIND to date. Due to the significant heterogeneity in the pathogenesis, clinical features, and prognosis of VCIND, clinical drug trials evaluating this disorder may need to focus on a particular subtype to obtain an accurate efficacy evaluation. VCIND caused by subcortical ischemic small vessel disease (hereinafter, subcortical VCIND) is a common subtype of VCIND and is considered relatively homogeneous in terms of its clinical and neuroimaging features. Therefore, it is suitable as a specific target for therapeutic trials investigating VCIND [7].

DL-3-n-butylphthalide (NBP) (Fig. 1) is a synthetic chiral compound containing L- and D-isomers of butylphthalide. It is developed from L-3-n-butylphthalide, which was initially isolated as a pure component from seeds of *Apium graveolens* in 1978 by researchers of Institute of Medicine of Chinese Academy of Medical Sciences. Studies in the past several decades have demonstrated that NBP is effective in protecting against ischemic cerebral injury, including inhibiting platelet aggregation, alleviating oxidative damage and mitochondria dysfunction in middle cerebral artery occlusion rats, improving microcirculation in focal cerebral ischemia rats, and reducing neurologic deficit after stroke in spontaneously hypertensive rats [8–13]. NBP was approved by the State Food and Drug Administration of China (SFDA) as a therapeutic drug for treatment of ischemic stroke in 2005 based on the results of the multicentre phase 2 and 3 randomized controlled clinical trials, which consistently reported that NBP was effective in improving neurologic function after stroke, with a good safety and tolerability [14,15]. Not only for ischemic stroke, NBP has been reported to increase the expression of NR2B and synaptophysin in hippocampus of aged rats after chronic cerebral hypoperfusion and increasing brain acetylcholine level, which are important processes involved in learning and memory [16,17]. It could alleviate the learning and memory deficits induced by cerebral ischemia in rats [18]. The pathogenesis of subcortical VCIND involved ischemic cerebral injury and microcirculation dysfunction, which are the action targets of NBP [19,20]. Hence, we hypothesized that NBP may have therapeutic efficacy for patients with subcortical VCIND and designed the present study.

2. Methods

2.1. Study design and oversight

This was an investigator-initiated multicentre, randomized, placebo-controlled, double-blind, parallel group trial

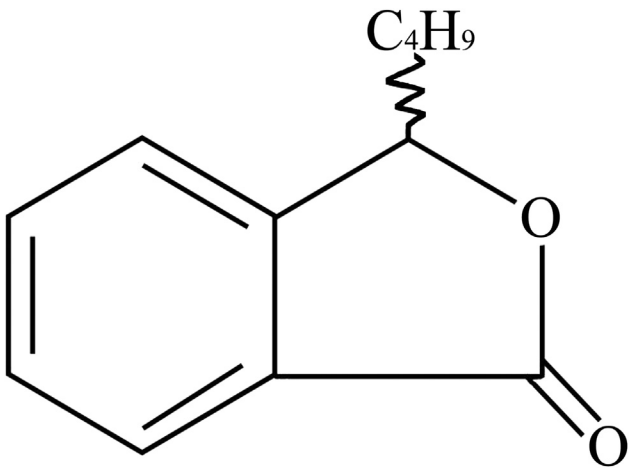

Fig. 1. Chemical structure of DL-3-n-butylphthalide (NBP). NBP is a novel synthetic chiral compound containing L- and D-isomers of butylphthalide.

that enrolled patients from 15 academic centers in China. The research protocol was approved by the institutional review board at each participating institution, and all participants provided written informed consent. The Shijiazhuang Pharmaceutical Group Company donated the study medication but had no other role in the study. An independent data and safety monitoring board was responsible for monitoring the conduct, safety, and the adherence to protocol of the trial. This study is registered in the Chinese Clinical Trial Registry, number ChiCTR-TRC-09000440.

2.2. Participants and eligibility criteria

We enrolled adults with a diagnosis of subcortical VCIND. Inclusion criteria were (1) literate Han Chinese, aged 50–70 years, with a consistent caregiver who accompanied the subjects at least 4 days a week; (2) complaint and/or informant report of cognitive impairment involving memory and/or other cognitive domains lasting for at least 3 months; (3) neither normal nor demented according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [21,22], with clinical dementia rating (CDR) $\geq$0.5 on at least one domain [23] and global score $\leq$0.5; a mini-mental state examination (MMSE) score $\geq$20 (primary school) or $\geq$24 (junior school or above) [24,25]; and (4) normal or slightly impaired activities of daily living (ADL) as defined by a total score of $\leq$1.5 on the three functional CDR domains (home and hobbies, community affairs, and personal care) [26]. All patients meeting the clinical criteria underwent brain magnetic resonance imaging (MRI) scan including hippocampal assessment at screening. The MRI entry criteria are as follows: (1) multiple ($\geq$3) supratentorial subcortical small infarcts (3–20 mm in diameter), with/without white matter lesions (WML) of any degree; or moderate to severe WML (score $\geq$ 2 according to the Fazekas rating scale) [27] with/without small infarct; or one or more strategically located subcortical small infarcts in the caudate nucleus, globus pallidus, or thalamus; (2) absence of cortical and watershed infarcts, hemorrhages, hydrocephalus, and WMLs with specific causes (e.g., multiple sclerosis); and (3) no hippocampal or entorhinal cortex atrophy (scored 0 according to medial temporal lobe atrophy scale of Scheltens) [28]. To minimize diagnostic variability, the current trial used a central neuroimaging reader to determine eligibility, ensuring consistent application of the criteria. Exclusion criteria included severe aphasia, physical disabilities, or any other factor that may preclude completion of neuropsychological testing; disorders other than subcortical VCIND that may affect cognition; the score of Hamilton depression scale >17, or schizophrenia; new strokes within 3 months before baseline; inherited or inflammatory small vessel disease; clinically significant gastrointestinal, renal, hepatic, respiratory, infectious, endocrine, or cardiovascular system disease; cancer; alcoholism; drug addiction; use of medications that may affect cognitive functioning, including tranquilizers, anti-anxiolytics, hypnotics, nootropics, and cholinomimetic agents; known hypersensitivity to celery; and inability to undergo a brain MRI.

2.3. Interventions

Patients were randomly assigned in a 1:1 ratio to receive three times daily oral NBP 200 mg or placebo of identical appearance for 24 weeks. The randomization list (stratified by investigation site, in blocks of four) was generated by an independent statistician. Every site was supplied with kits of study drug that were labeled with sequential numbers corresponding to the randomization list. When randomized, each successive participant was assigned to the lowest numbered kit in sequence at each site by the site investigator. Patients, caregivers, and site investigators were blinded to the treatment allocation. Compliance was assessed by counting unused capsules remaining in the medicine bottle.

2.4. Outcome measures

The primary outcome measures were the 12-item Alzheimer's disease assessment scale-cognitive subscale (ADAS-cog) [29] and the clinician's interview-based impression of change plus caregiver input (CIBIC-plus) [30]. The ADAS-cog is a composite of individual and independently valid measures which evaluates six areas of cognition (memory, language, orientation, reason, praxis, and concentration). The total score ranges from 0 to 75, with lower scores indicating lesser severity. The CIBIC-plus reflects the clinical improvement of a subject based on interviews with that subject and his/her caregiver. It is scored on a seven-point scale ranging from 1 to 7, where 1 represents maximum improvement, 4 no change, and 7 maximum worsening. The clinician's interview-based impression of severity (scored 0–7, with higher scores indicating worse functioning) at baseline was used as a reference for subsequent CIBIC-plus ratings. The clinician completing

the CIBIC-plus was blind to the other psychometric assessments and adverse events (AEs). The secondary measures were the MMSE [24], a 30-point scale that measures cognitive function, with higher scores indicating better function; CDR [23], a multidimensional scale for dementia severity, which scored 0–3, with higher scores indicating worse functioning; the sum of boxes of the CDR (CDR-sb), which scored 0–18, with higher scores indicating worse functioning; the Chinese version of the ADL scale [31], which included basic ADL and instrumental ADL to assess patient's daily living ability (scored 20–80, with higher scores indicating worse functioning); and the neuropsychiatric inventory (NPI), which assesses 12 neuropsychiatric abnormalities. The total score ranges from 0 to 144, with higher scores indicating greater impairment [32].

Safety measures included physical examinations, vital signs, electrocardiography, laboratory tests (hematologic tests, blood chemical values, urinalysis, and stool analysis), and AEs records. Efficacy and safety measures were assessed at baseline and at weeks 12 and 24. All interviewers and experts received uniform training on the standard administration of assessment tools and diagnosis. The interrater reliability for cognitive tests and diagnosis, which relied on videotaped interviews, was required to exceed 0.90. All trainees had to pass examinations for consistency before being allowed to participate in the study.

2.5. Statistical analysis

The power of this study was calculated based on the primary end point, change from baseline on ADAS-cog. Because the clinical use of NBP in VCIND patients is still in the exploratory stages and no previous trial results were available, a review of the results of clinical trials of donepezil in patients with MCI was used as a reference for sample size calculation, which is the most evaluated agent in MCI population [26,33]. The two-sided t test with a significance level of 5% was used, and the standard deviation (SD) was assumed to be 4.2 for the change from baseline in ADAS-cog. A total of 192 patients (96 per group) were needed to achieve 80% power to detect a 1.7-point drug-placebo difference in change from baseline on the ADAS-cog. Given an expected dropout of 20%, the total number of patients to be randomized was increased to 240.

The primary and secondary outcome measures were analyzed using data from the intention-to-treat (ITT) population and the per protocol population. In this study, the ITT population consisted of all randomized patients who received at least one dose of trial medication and had a complete baseline assessment as well as at least one post-treatment assessment for the primary outcome variables. For the ADAS-cog and secondary measures, missing values were replaced using the last observation carried forward method. For the CIBIC-plus, missing observations were replaced with the median score of 4 (i.e., unchanged) [34]. The per protocol population included patients who completed the 24-week treatment and evaluation as planned with no major protocol violations.

ADAS-cog (including the monomial item of the ADAS-cog) changes from baseline, CIBIC-plus global score, and the secondary efficacy variables were assessed using an analysis of covariance with treatment groups and centers as factors and baseline values as covariates. Standardized mean differences were used to express effect sizes in SD. The CIBIC-plus category was analyzed as categorical data using the Cochran-Mantel-Haenszel (CMH) procedure stratified by centers.

The baseline homogeneity of the baseline characteristics between the two groups were analyzed with Fisher's exact test, the χ^2 test, or the CMH test for categorical measures and with the t test or Wilcoxon rank-sum test for continuous measures. The safety population consisted of all subjects who took at least one dose of the study medication with at least one postbaseline safety evaluation. The χ^2 or Fisher's exact test was used to analyze AEs incidences. All analyses were done with SAS 9.1.3 (SAS Institute, Cary, NC, USA). All hypothesis tests were two-tailed, and P values $\leq .05$ were considered significant.

3. Results

3.1. Patients

Between September 2008 and December 2009, 563 patients were screened for study participation and 281 underwent randomization. Fig. 2 summarizes patient recruitment, participation, and attrition. Baseline characteristics between study groups were similar (Table 1). The clinical profiles of the enrolled patients were highly consistent with a diagnosis of subcortical VCIND, as evidenced by high rates of hypertension and history of ischemic stroke. Most enrolled patients (86.8%) were taking concomitant medications, with the most common being aspirin, antihypertensive agents, and lipid-reducing agents. There were no significant differences between treatment groups in the level of blood pressure, blood glucose, and blood lipid during the treatment (Tables S1–S9).

3.2. Outcomes

In the ITT analysis, a significant treatment difference at week 24 favoring NBP was observed on ADAS-cog (Table 2). The adjusted mean change from baseline in ADAS-cog at week 24 was −2.46 for the NBP group and −1.39 for the placebo group (drug-placebo difference: −1.07 points; 95% confidence interval [CI], −0.12 to −2.02; $P = .03$; Fig. 3A). The effect size of the mean difference between drug and placebo group is 0.26 SD. A more favorable drug-placebo difference was seen in the per protocol population, with a 1.21-point difference in the ADAS-cog change from baseline ($P = .02$; Table S10). For the monomial item of the ADAS-cog, word recall scores in the NBP group improved significantly at week 24 relative

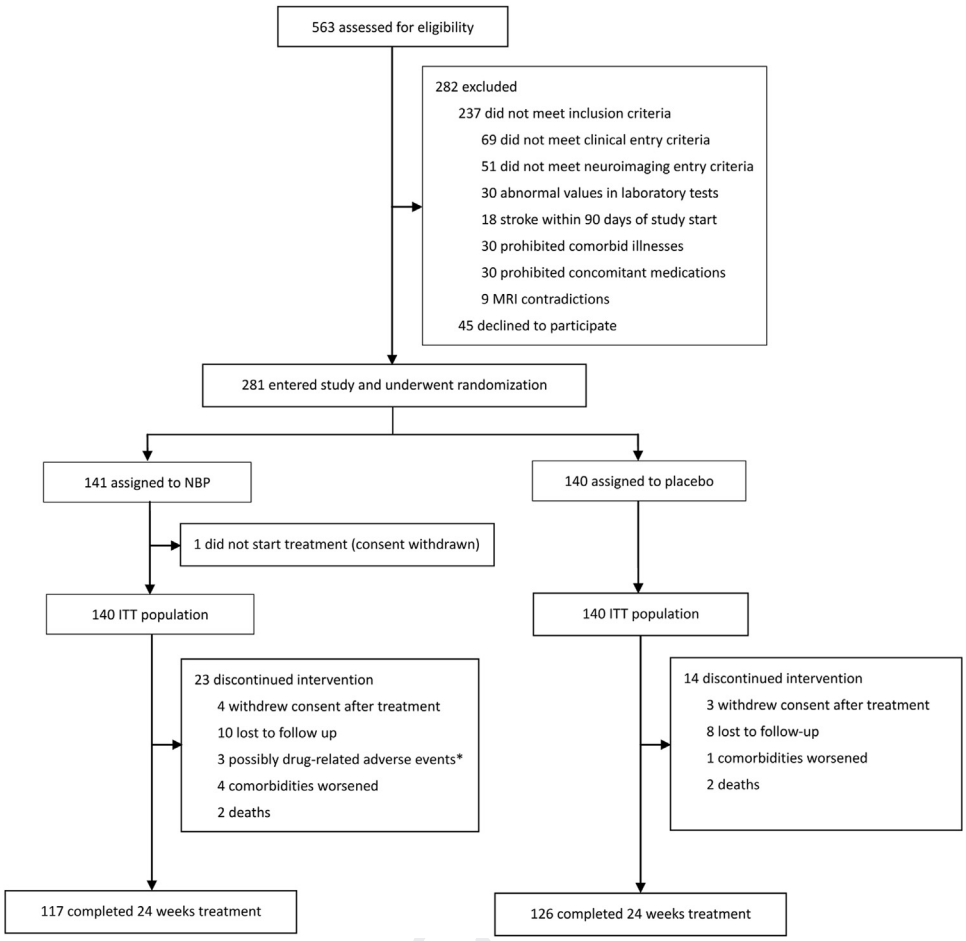

Fig. 2. Trial profile. ITT denotes intention-to-treat. *Adverse events defined as possibly drug-related include those thought to be possibly and probably drug related.

to the placebo group (NBP change −0.76 vs. placebo −0.23; $P = .002$; ITT analysis). There was no significant difference in other monomial items of ADAs-cog between NBP and placebo group. A CIBIC-plus score was used as a measure of overall clinical response to study medication. The CIBIC-plus ratings at week 24 were significantly better in the NBP group than those in the placebo group. The mean CIBIC-plus global score at week 24 was 3.24 for the NBP group and 3.53 for the placebo group (drug-placebo difference: −0.29 points; 95% CI, −0.48 to −0.10; $P = .003$; Fig. 3B). The effect size is 0.35 SD. For the per protocol population, the treatment difference was larger (drug-placebo difference: −0.33 points; $P < .001$). A CMH analysis of the CIBIC-plus ratings at week 24 revealed that 57.1% of the patients in the NBP group of the ITT population were rated as improved versus 42.1% of patients in the placebo group. Fig. 3C provided the distribution of CIBIC-plus ratings of ITT population at week 24. The ITT and per protocol analysis at week 24 did not reveal any significant differences between treatment groups in scores on the MMSE, CDR, CDR-sb, ADL, and NPI (Table 2 and Table S10).

3.3. Safety

Overall, 17.5% of patients experienced at least one AE during the study (NBP, 21.4%; placebo, 13.6%; $P = .08$; Table 3). Most AEs were mild-to-moderate in severity and were either not related or unlikely to be related to the study medication. AEs were possibly/probably related to the study drug in nine patients (NBP, five [3.6%]; placebo, four [2.9%]; $P = 1.00$) and were mostly mild gastrointestinal reactions (NBP, four [2.9%]; placebo, two [1.4%]; $P = .68$) and slight elevation of aminotransferase (NBP, one [0.7%]; placebo, two [1.4%]; $P = 1.00$). Three premature discontinuations were due to possible/probable drug-related gastrointestinal reactions in the NBP group. Serious AEs (SAEs) were reported in 12 patients (NBP, seven [5.0%]; placebo, five [3.6%]; $P = .56$). Four deaths were observed during the study (NBP, two; placebo, two). All SAEs, including the four deaths, were considered unrelated to the study medication. Additionally, no clinically meaningful changes from baseline were observed in any of the biochemical markers, vital signs, or electrocardiography results in either group.

Table 1
Baseline characteristics of participants by treatment group*

Characteristic	NBP (n = 140)	Placebo (n = 140)
Age, mean (SD), y	68.0 (8.8)	66.7 (7.7)
Female, n (%)	48 (34.3)	48 (34.3)
Education, n (%), y		
≤5	50 (35.7)	52 (37.1)
>5	90 (64.3)	88 (62.9)
Medical history, n (%)		
Hypertension	98 (70.0)	92 (65.7)
Hyperlipidemia	35 (25.0)	30 (21.4)
Diabetes mellitus	26 (18.6)	24 (17.1)
Atrial fibrillation	5 (3.6)	3 (2.1)
Ischemic stroke	104 (74.3)	109 (77.9)
Transient ischemic attack	16 (11.4)	13 (9.3)
Coronary heart disease	29 (20.7)	25 (17.9)
Concomitant drugs, n (%)		
Medications of all categories	122 (87.1)	121 (86.4)
Antihypertensive agents	83 (59.3)	86 (61.4)
Aspirin	86 (61.4)	92 (65.7)
Lipid-reducing agents	67 (47.9)	62 (44.3)
Hypoglycemic agents	24 (17.1)	21 (15.0)
Cardiac therapy†	24 (17.1)	22 (15.7)
Psychometric scores, mean (SD)		
ADAS-cog	14.07 ± 6.33	13.97 ± 6.58
CIBIS	2.33 ± 0.50	2.30 ± 0.46
MMSE	25.01 ± 2.49	25.18 ± 2.37
CDR	0.50 ± 0.04	0.50 ± 0.00
CDR-sb	1.62 ± 0.85	1.69 ± 0.90
ADL	24.49 ± 6.30	24.36 ± 5.14
NPI	2.11 ± 2.99	2.32 ± 3.95
HAMD	3.84 ± 2.36	3.96 ± 2.39

Abbreviations: NBP, dl-3-n-butylphthalide; SD, standard deviation; ADAS-cog, Alzheimer's disease assessment scale-cognitive subscale; CIBIS, clinician interview-based impression of severity; MMSE, mini-mental state examination; CDR, clinical dementia rating scale; CDR-sb, the sum of boxes of the CDR; ADL, activities of daily living scale; NPI, neuropsychiatric inventory; HAMD, Hamilton depression scale.

*There were no significant differences among the groups in any of the baseline characteristics.

†Cardiac therapy includes glycosides and nitrates.

4. Discussion

VCIND is the earliest possible, and likely the optimal, stage for the introduction of anti-dementia agents. As the first multicentre, randomized, double-blind, placebo-controlled trial focusing on VCIND, this study should be considered exploratory. The methods and findings of the present study may contribute important insights into patient selection, outcome measures, sample and effect sizes, and study duration of VCIND drug trials. The results may provide a promising treatment option for this disorder.

This trial used an innovative and careful design. First, most previous drug trials in VaD did not control the heterogeneity of enrolled subjects adequately and the results may thus have had bias from the inherent sample inhomogeneity [35]. By targeting patients with subcortical VCIND, the present study could evaluate whether a particular subgroup could benefit from a specific medication without the treatment effect's being compromised by heterogeneity within the sample. Second, this study adopted a stringent neuroimaging criteria. The selection for subcortical VCIND was ensured by the requirement of subcortical small infarcts and/or WMLs identified on MRI. Because of the high prevalence of Alzheimer's disease (AD) in elderly people, to exclude the influence of coexistent early AD pathology remains crucial in VCIND trials. By excluding patients who exhibited hippocampal or entorhinal cortical atrophy on MRI, the results excluded treatment effects influenced by coexisting AD pathology as much as possible. Third, although VCIND has been recognized as an at-risk state for dementia, the cognitive impairment of VCIND is not always progressive. Alike to MCI, VCIND includes a predementia group and a group remaining cognitively stable or reverting to normal at follow-up [1]. To reveal the true and accurate efficacy of an anti-dementia medication, only those VCIND patients who are invariably progressing toward dementia are best candidates. Longitudinal research suggested that subcortical VCIND is at a predementia stage with a high risk of adverse outcomes, making this population suitable for intervention trials of VCIND [36]. In addition, the impact of poststroke recovery is an important issue that should be addressed in the design of anti-dementia drug trials. Previous VaD trials suggest that subjects with recent stroke were likely to improve on placebo [37], thus patients who showed fresh infarction on MRI diffusion weighted imaging or experienced strokes in recent 3 months were excluded from the present study. The patient selection protocol of current trial would maximally ensure that the observed effect is a consequence of treatment rather than spontaneous recovery.

We demonstrated a favorable effect of NBP in treatment of patients with subcortical VCIND as measured by ADAS-cog and CIBIC-plus. A drug-placebo difference of 1.07 was observed on the ADAS-cog in the present study, which fell within the typical results of the previous VaD trials, i.e., around 1–2 points drug-placebo differences on ADAS-cog [35,37–39]. Because of the mild magnitude of cognitive decline, there leaves little room to detect a cognitive improvement in MCI trials. In the early stages of the disease, the natural decline of cognition associated with VCIND is thought to be slower than that in VaD, which renders the demonstration of a treatment effect more difficult. Nevertheless, a drug-placebo difference of 1.07 was observed on the ADAS-cog in the present study. The size of the treatment effect was also calculated as a standardized effect size. The effect size of drug-placebo mean difference on ADAS-cog is 0.26 SD, which is larger than that for rivastigmine trial in VaD (0.15 SD on the ADAS-cog) and comparable with that of one donepezil trial in VaD (0.22 SD on the ADAS-cog) [38,40]. The clinical meaningfulness of the improvement on ADAS-cog is further supported by convergence within ADAS-cog and CIBIC-plus. The mean CIBIC-plus score was significantly better for the NBP than for the placebo group and a higher percentage of patients were rated as improved in the NBP

Table 2
Efficacy outcomes in ITT population at week 24

Psychometric scores	Adjusted mean (SE) change from baseline		Difference in adjusted mean (95% CI)	*P* value
	NBP (n = 140)	Placebo (n = 140)		
ADAS-cog	−2.46 ± 0.35	−1.39 ± 0.35	−1.07 (−2.02 to −0.12)	.03
CIBIC-plus global score	3.24 ± 0.07	3.53 ± 0.07	−0.29 (−0.48 to −0.10)	.003
MMSE	1.51 ± 0.19	1.26 ± 0.18	0.26 (−0.25 to 0.76)	.32
CDR	−0.05 ± 0.01	−0.02 ± 0.01	−0.02 (−0.06 to 0.02)	.22
CDR-sb	−0.03 ± 0.08	−0.07 ± 0.07	0.04 (−0.16 to 0.24)	.70
ADL	−0.62 ± 0.33	−0.80 ± 0.33	0.18 (−0.70 to 1.07)	.69
NPI	−0.13 ± 0.17	−0.43 ± 0.17	0.29 (−0.15 to 0.74)	.19

Abbreviations: ITT, intention-to-treat; NBP, dl-3-n-butylphthalide; SE, standard error; CI, confidence interval; ADAS-cog, Alzheimer's disease assessment scale-cognitive subscale; CIBIC-plus, clinician's interview-based impression of change plus caregiver input; MMSE, mini-mental state examination; CDR, clinical dementia rating scale; CDR-sb, the sum of boxes of the CDR; ADL, activities of daily living scale (Chinese version); NPI, neuropsychiatric inventory.

group, which indicates that the drug-placebo difference on ADAS-cog, although small, is clinically meaningful to this population with mildly impaired cognition. When interpreting the clinical meaningfulness of the score improvement on ADAS-cog, it is important to recognize that the cognitive declines of VCIND patients are subtle enough that its clinical progression within 6 months may even not be considered clinically relevant if it is quantized using conventional assessment tools. Compared to those with dementia, the same magnitude of cognitive improvement as measured by quantitative scale may have more clinical meanings for mildly impaired patients. Thus the clinical relevance of the gain on cognitive measures, even of small size, should not be ignored in MCI trials.

Throughout this study, the cognitive function of placebo-treated patients did not decline as expected. Thus, the observed drug-placebo differences were largely derived from greater improvements in the NBP group relative to the impact seen in the placebo group. The absence of decline in the placebo group may have resulted from the following: (1) VCIND itself was at a slowly progressing stage and a longer time period may be necessary to identify the cognitive decline; (2) the presence of a placebo effect. Other reasons may include practice effects in this subtly impaired population and the exclusion of significant comorbidities that likely determines faster progression.

Several pathogenic mechanisms including acute infarction, chronic ischemia, oxidative stress, and microcirculation dysfunction may converge to cause subcortical VCIND [7,19,41,42]. The efficacy of NBP on subcortical VCIND may be mediated by multiple targets involved in the pathogenesis of this disorder. Data from animal models suggest that NBP exerts its effects on ischemia-induced cognitive deficits by preventing ischemic neuropathologic alterations, increasing acetylcholine synthesis, and inhibiting oxidative damage [43,44]. Additionally, NBP has been shown to reduce the size of WML and cerebral infarctions, which constitute the main pathologic substrate of subcortical VCIND [12,44]. In future studies, we may need to use neuroimaging assessment before and after intervention to explore the mechanisms underlying the efficacy of NBP on subcortical VCIND, and whether it has a potential for disease modification.

Because of the scarcity of data on natural course of VCIND, and the shortage of drug trials dedicated to it; currently, there is no consensus regarding the optimal duration for intervention trials investigating VCIND. Interventional trials of MCI with symptomatic effect as a primary objective are generally shorter, usually 6–12 months. Results from previous trials have demonstrated that it is possible to detect the symptomatic effects of anti-dementia agents in MCI patients within 6–12 months [26,45,46]. This preliminary study is designed for 24 weeks, and the results demonstrated that it is possible to detect the symptomatic effects of NBP in subcortical VCIND within this period, even with the presence of a placebo effect. Nevertheless, given the lack of deterioration in the placebo group, and the small drug-placebo difference observed, a treatment period of 6 months is suboptimal. An adequately designed study lasting for 2–5 years will be necessary to fully explore the symptomatic efficacy of NBP in this disorder as well as its efficacy on prevention of dementia.

The attempts to develop new treatments for cognitive impairment of vascular origin have been fraught with lengthy time, expensive costs, and high failures rates. Repurposing of older drugs to new indication might provide a lower risk alternative [47]. NBP was initially approved by SFDA for treatment of stroke in 2005. Evidence of previous studies supported the rationality of repurposing NBP for treatment of subcortical VCIND [16,18–20]. Such a "drug repurposing" approach has several advantages, including the established safety profile of the drug and reduction of time and costs for clinical trials. NBP was safe and well tolerated in this study sample. The drug-related AEs were mostly mild gastrointestinal symptoms and slight elevation of aminotransferase and occurred at a very low frequency (4%). This is consistent with the known safety profile of NBP in treatment of ischemic stroke [14,15]. No unexpected side effects were observed.

Several limitations of the study must be mentioned. The outcome measures adopted by the present study may not

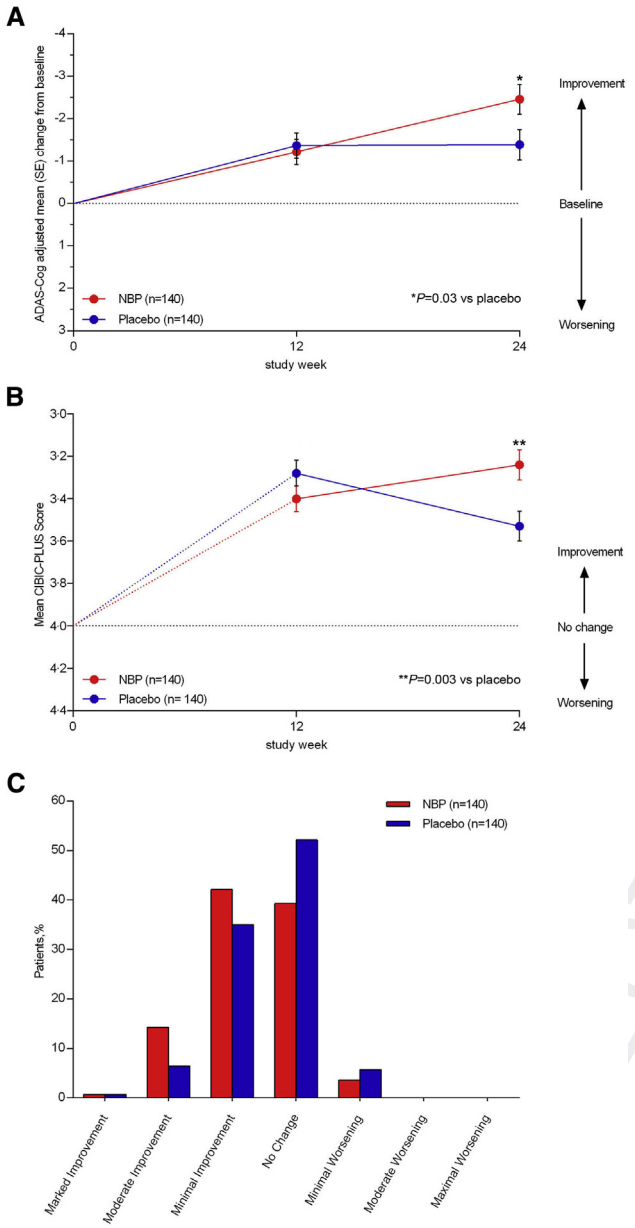

Fig. 3. Primary outcome measures in the intention-to-treat (ITT) population. (A) Alzheimer's disease assessment scale-cognitive subscale (ADAS-cog) adjusted mean (±SE) change from baseline of ITT population at weeks 12 and 24. Missing values for ADAS-cog were replaced by use of the last observation carried forward (LOCF) method. (B) Clinician's interview-based impression of change plus caregiver input (CIBIC-plus) mean score (±SE) of ITT population at weeks 12 and 24. Missing values for CIBIC-plus were replaced by median score of 4. (C) Distribution of CIBIC-plus ratings of ITT population at week 24. $P = .005$ for the comparison between the distribution of values for the NBP and placebo groups, determined by Cochran-Mantel-Haenszel procedure stratified by centers. Missing values for CIBIC-plus were replaced by median score of 4. Abbreviations: SE, standard error; NBP, dl-3-n-butylphthalide.

be sufficiently sensitive to detect changes in cognition and function at a stage of the disease characterized by mild impairments. A small change in the ADAS-cog could therefore be partially due to its insensitivity for the study population. Another limitation is that the cognitive assessment batteries used did not pay more attention to executive dysfunction which is common in subcortical ischemic small vessel disease, and the treatment effects thus might have been underestimated. In addition, the brain MRI was performed only at baseline to confirm the diagnosis but not at 24 weeks, thus not allowing the use of neuroimaging as a surrogate marker to assess treatment effects. Finally, the methodology of sample size calculation should be improved. Compared to the actually observed improvement on ADAS-cog, we overestimated the drug-placebo difference when working on sample size calculation at the planning of the clinical trials. Thus, the sample size was underestimated, and the desired power was not achieved. An adequately powered trial with larger sample size is necessary to further verify the results in the future.

5. Conclusions

In summary, this preliminary study suggested that NBP treatment of 6 months is effective in improving the cognition and global functioning of patients with subcortical VCIND, providing a promising option for early intervention of this disorder. Future trials with longer duration and larger sample size to further test the efficacy of NBP on subcortical VCIND or a broader VCIND cohort are warranted.

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Table 3
Patients experiencing adverse events

Event	NBP (n = 140)	Placebo (n = 140)	*P* value
Adverse events, number of patients with event (%)	30 (21.4)	19 (13.6)	.08
Adverse events occurring in at least two patients in either treatment group, n (%)			
Increase total cholesterol/triglycerides level	10 (7.1)	4 (2.9)	.10
Abnormal liver enzymes	1 (0.7)	2 (1.4)	1.00
Mild gastrointestinal intolerance	4 (2.9)	2 (1.4)	.68
Ischemic stroke	2 (1.4)	3 (2.1)	1.00
Urinalysis abnormalities	2 (1.4)	0	.48
Dizziness	2 (1.4)	0	.48
Death	2 (1.4)	2 (1.4)	1.00
Possibly drug-related adverse events, n (%)*	5 (3.6)	4 (2.9)	1.00
Mild gastrointestinal intolerance	4 (2.9)	2 (1.4)	.68
Abnormal liver enzymes	1 (0.7)	2 (1.4)	1.00
Drug-related adverse events resulting in treatment discontinuation, n (%)	3 (2.1)	0	.25
Mild gastrointestinal intolerance	3 (2.1)	0	.25
Adverse events affecting the cerebrovascular system, n (%)	4 (2.9)	4 (2.9)	1.00
Ischemic stroke	2 (1.4)	3 (2.1)	1.00
Transient ischemic attack	1 (0.7)	0	.50
Hemorrhagic stroke	1 (0.7)	1 (0.7)	1.00
Any serious adverse events, n (%)	7 (5.0)	5 (3.6)	.56
Myocardial infarction	1 (0.7)	0	.50
Arrhythmia	0	1 (0.7)	.50
Ischemic stroke	2 (1.4)	3 (2.1)	1.00
Hemorrhagic stroke	1 (0.7)	1 (0.7)	1.00
Bone fracture	1 (0.7)	0	.50
H1N1 influenza A	1 (0.7)	0	.50
Death	2 (1.4)	2 (1.4)	1.00

*Adverse events defined as possibly trial-drug related include those thought to be possibly and probably drug related.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jalz.2015.04.010.

RESEARCH IN CONTEXT

1. Systematic review: We searched PubMed for randomized placebo-controlled drug studies in vascular cognitive impairment no dementia (VCIND) published before November 25, 2014. The resulting articles were manually reviewed. Only two reports were identified: a Chinese study that assessed the efficacy of a 16-week treatment with modified shuyu pill on VCIND in a series of 100 patients [48] and a Singapore study that assessed the efficacy of a 24-week treatment with rivastigmine on VCIND in a small series of 50 patients [49]. We did not find any multicentre trial on VCIND or any drug studies focusing on subcortical VCIND.
2. Interpretation: In this multicentre, randomized, double-blind, placebo-controlled study, we assessed the effectiveness of dL-3-n-Butylphthalide (NBP) in improving cognitive function of patients with subcortical VCIND. This study is the first multicentre drug trial on VCIND and the first drug trial focusing on subcortical VCIND to date. The findings demonstrate that NBP is a promising therapeutic approach for subcortical VCIND. Our work may contribute important insights into the design of future VCIND drug trials.
3. Future directions: Future trials with longer duration and larger sample size to further test the efficacy of NBP on subcortical VCIND or a broader VCIND cohort are warranted.

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