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# Efficacy and safety of early butylphthalide initiation in acute ischemic stroke: A multicenter, randomized, clinical trial (BENEFIT) protocol

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### *Abstract*

*Background:* Acute ischemic stroke (AIS) is a major cause of disability and death worldwide. While time windows for reperfusion therapies are well defined, the optimal timing for neuroprotective agents remains unknown. This study aims to investigate whether early initiation (<3 hours) of DL-3-n-butylphthalide (NBP), a promising neuroprotective agent, leads to better outcomes compared to late initiation (3-6 hours) in AIS patients. *Methods:* This study is an exploratory, prospective, multicenter, randomized, open-label trial with blinded endpoint assessment. The study plans to recruit approximately 200 AIS patients presenting within 3 hours of symptom onset from around 20 stroke centers in China. Patients will be randomized in a 1:1 ratio into either the early group (<3 hours of intravenous NBP administration) or the late group (3–6 hours of intravenous NBP administration). The treatment regimen consists of 100 mL of NBP administered intravenously twice daily for 12±2 days. The primary objective of the study is to evaluate the efficacy and safety of early versus late intravenous administration of NBP in AIS patients and to explore the optimal therapeutic time window for neuroprotection. The primary outcome is the proportion of patients achieving an excellent functional outcome, defined as a modified Rankin Scale (mRS) score of 0–2, at 90±7 days post-randomization. Secondary outcomes include changes in stroke severity scores, rates of neurological deterioration, stroke recurrence, and safety outcomes.
*Conclusion:* This trial will provide valuable evidence for the efficacy and safety of early versus late initiation of intravenous NBP for improving 90-day functional outcomes in patients with AIS. This trial will provide evidence regarding the optimal timing of neuroprotective therapy in AIS and potentially establish a new therapeutic paradigm.
Registration details: ClinicalTrials.gov (NCT06472921), registered on June 19, 2024.

*Keywords:* Acute ischemic stroke, neuroprotection, butylphthalide, randomized controlled trial, time factors

## INTRODUCTION

Acute ischemic stroke (AIS) remains a leading cause of disability and mortality worldwide, with an estimated global prevalence of 101 million stroke survivors in 2021, of which approximately 80% are ischemic stroke cases.[1] Despite advances in reperfusion therapies, including intravenous thrombolysis and endovascular thrombectomy,

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many patients still experience poor outcomes[2], highlighting the critical need for additional therapeutic strategies, particularly neuroprotective interventions.

The history of neuroprotection in stroke treatment reveals a challenging landscape. Despite thousands of preclinical studies and hundreds of clinical trials on neuroprotective agents over the past decades[3], few have demonstrated efficacy in confirmatory phase III trials.[4] A systematic review and recent clinical evidence suggest that a key factor contributing to these failures is the narrow therapeutic window for neuroprotection in the ischemic penumbra, typically less than 2-3 hours.[5,6] A comprehensive analysis of previous trials revealed that less than 2% of patients received study drugs within this crucial timeframe.[6-8]

DL-3-n-butylphthalide (NBP), a novel neuroprotective agent derived from celery seeds, has emerged as a promising therapeutic option. Its multiple mechanisms of action include improving cerebral microcirculation, reducing blood-brain barrier permeability, inhibiting inflammatory responses, and promoting neurogenesis.[9,10] The BAST trial demonstrated that NBP significantly improved functional outcomes in AIS patients who received reperfusion therapy[11], making it an ideal candidate for investigating the impact of treatment timing on neuroprotective efficacy.

While the optimal therapeutic time windows for reperfusion therapies are well-established, the timing-dependent efficacy of neuroprotective agents remains largely unexplored. This knowledge gap is particularly significant for NBP, as the optimal timing for its administration in AIS patients has not been systematically evaluated.[12] Based on the "time is brain" concept and the narrow therapeutic window observed in previous neuroprotection studies[6,13,14], we hypothesize that earlier administration of NBP (<3 hours from symptom onset) will result in better functional outcomes compared to later administration (3-6 hours).

The primary objective of the BENEFIT trial is to evaluate the efficacy and safety of early (<3 hours) versus late (3-6 hours) initiation of intravenous NBP in AIS patients in order to determine the optimal therapeutic window for neuroprotection. These objectives align with contemporary stroke research priorities and address critical gaps in understanding the timing of neuroprotective interventions.

The potential impact of this trial extends beyond its immediate objectives. Establishing the optimal timing for NBP administration could lead to more cost-effective treatment strategies and inform guidelines on the prioritization of acute stroke interventions.[15] The comprehensive dataset generated will contribute significantly to our understanding of stroke pathophysiology and recovery.

## METHODS

### *Study design*

The Efficacy and Safety of Early Butylphthalide Initiation in Acute Ischemic Stroke (BENEFIT) study is a multicenter prospective, randomized, open-label, blinded-endpoint (PROBE) trial to be conducted in 20 stroke centers across China. The study protocol was approved by the Ethics Committee of Xiangya Hospital, Central South University (Approval No. 202405104). Written informed consent will be obtained from all participants or their authorized representatives. Block randomisation by four will be used to allocate enrolled participants into one of two arms. Participants will be randomly assigned to either early initiation group (<3 hours) or late initiation group (3-6 hours) according to a 1:1 allocation ratio. Assessors responsible for evaluating the neurological outcomes at baseline, 24±2 hours, 6±1 days, 12±2 days, and 90±7 days will be blinded to treatment allocation. Table 1 summarizes the measures collected during each visit.

The study intervention will be delivered through intravenous administration of NBP sodium chloride injection at participating stroke centers. Treatment compliance will be monitored through daily documentation in electronic case report forms (eCRF). Our study is scheduled to commence on 1 July 2024 and conclude on 31 December 2025. The analysis is expected to be completed by December 2025. Figure 1 presents a diagram of the overall study design.

### *Recruitment strategy and sample selection*

Each participating center will implement a standardized screening process in their emergency departments. Site investigators will work closely with emergency medicine physicians to identify potential participants. Regular recruitment updates will be provided to all sites, with additional support provided to sites with lower enrollment rates. A central recruitment coordinator will monitor screening logs and provide feedback to optimize recruitment strategies.

**Table 1: Schedule of assessments and measures collected at each study visit**

| Measures | Visit 1 | Visit 2 | Visit 3 | Visit 4 | Visit 5 |
|---|---|---|---|---|---|
| Time | Baseline | 24±2h | 6±1d | 12±2d | 90±7d |
| Demographics[1] | X | | | | |
| Medical history | X | | | | |
| mRS score | X[&] | | | | X |
| Current medication | X | | | | |
| Clinical examination[2] | X | X | X | X | |
| NIHSS score | X | X | X | X | |
| Head CT | X | | | X^ | |
| Brain MRI | | | | X[#] | |
| ASPECTS score | X[%] | | | | |
| Reperfusion therapy assessment | | X | | | |
| Reperfusion method and time | | X | | | |
| mTICI Grade | | X | | | |
| Laboratory tests | | X* | | | |
| 12-Lead ECG | X | | | | |
| Verify inclusion/exclusion criteria | X | | | | |
| Informed consent | X | | | | |
| Randomization | X | | | | |
| Study drug administration | X | | | | |
| Biomarker blood sampling[3] | X | X | X | | |
| TOAST classification | | | | X | |
| CISS classification | | | | X | |
| EQ-5D scale | | | | | X |
| AE/SAE | | X | X | X | X |
| Concomitant Medication | X | X | X | X | X |

1. Including: gender, age, education, occupation, etc.
2. Including: vital signs and physical examination
3. All samples will be properly handled and disposed of by Xiangya Hospital, Central South University. Participants will not incur any costs for this procedure &. Refers to pre-stroke mRS score
%. If baseline CT perfusion is performed, relevant results should be collected
*. Including: blood routine, urinalysis, coagulation profile, fasting blood glucose, liver and kidney function (including creatinine, transaminases), electrolytes, lipids, cardiac enzymes and homocysteine
^. If baseline CT perfusion was performed, plain CT scan should be completed at Visit 4. Relevant indicators can be collected and recorded
#. Within 12±2 days after randomization, patients need to complete: T1+T2+DWI sequence. See imaging collection manual for details

Patient eligibility is determined based on pre-specified inclusion and exclusion criteria. Eligible patients must be 18-80 years old with a clinical diagnosis of acute ischemic stroke, presenting within 3 hours of symptom onset. Additional inclusion criteria comprise a baseline NIHSS score of 4-25, pre-stroke modified Rankin Scale score of 0-1, and ability to provide informed consent. Key exclusion criteria include recent intracranial hemorrhage, severe organ dysfunction, uncontrolled blood pressure (systolic <90 mmHg or >220 mmHg), significant cardiac conditions, history of hemorrhagic diseases, pregnancy or breastfeeding, severe mental disorders, and concurrent participation in other clinical trials. Patients can be enrolled regardless of whether they receive reperfusion therapy or the specific type of reperfusion therapy. The complete list

of exclusion criteria ensures patient safety and study validity. Additional inclusion and exclusion criteria are detailed in Figure 2.

*Randomization and blinding*

After emergency admission and inclusion procedure according to the study protocol, eligible patients with acute ischemic stroke will be randomized in two balanced parallel groups (1:1) to receive either early initiation (<3 hours) or late initiation (3-6 hours) of NBP treatment. Randomization will be performed using block randomization with a block size of 4, generated by SAS software. Each eligible subject will be assigned a unique screening number after signing the informed consent form and before any study-related examinations. Screening numbers must not be reused. After the subject passes screening, the investigator or designated personnel will obtain the randomization number and corresponding NBP initiation time group (early or late) through the randomization system. The investigator will then initiate NBP treatment according to the assigned group. This is an open-label trial for subjects and investigators, but the evaluators of neurological outcomes will be blinded. Subjects are enrolled and randomized by neurologists or other qualified investigators as specified in the study protocol.

*Intervention protocol*

The study drug is NBP Injection (25 mg Butylphthalide and 0.9 g Sodium Chloride

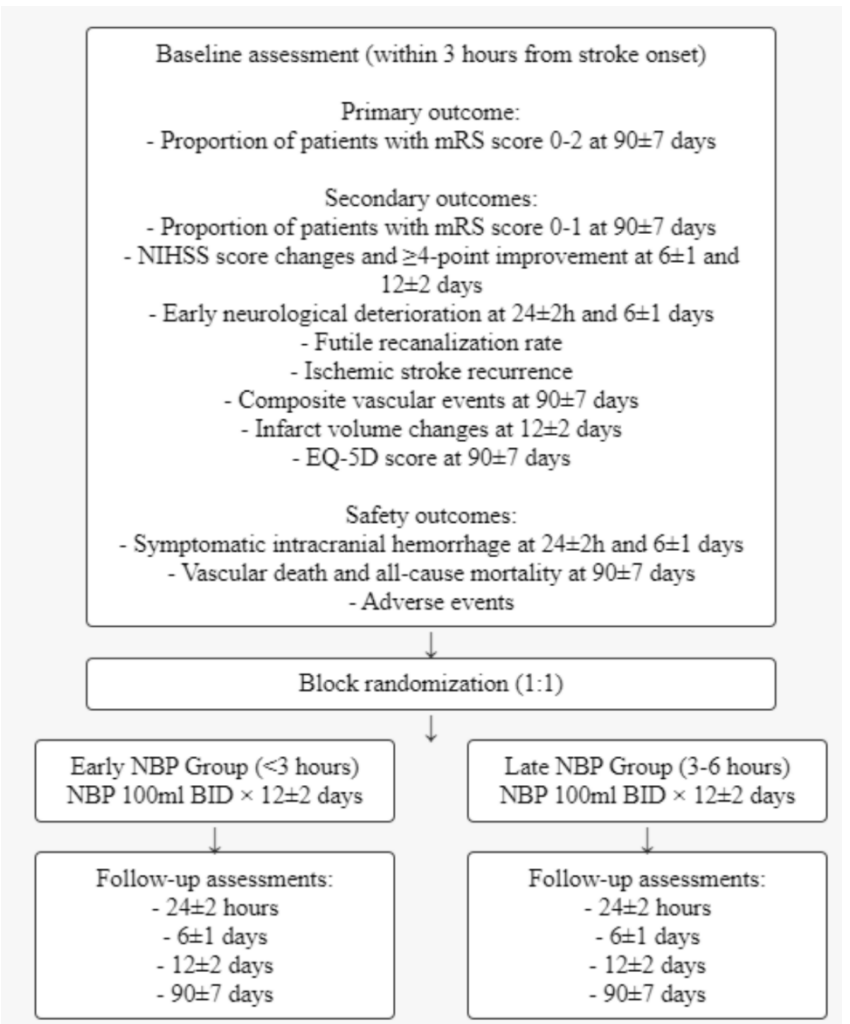


Figure 1. Study flow diagram of the BENEFIT trial

Abbreviation: mRS, modified Rankin scale; NIHSS, National Institutes of Health stroke scale; EQ-5D, EuroQol-5 dimension; BID, bis in die (twice a day); NBP, DL-3-n-butylphthalide.

| Inclusion criteria | Exclusion criteria |
|---|---|
| 1. Age 18-80 years<br>2. Clinical diagnosis of acute ischemic stroke<br>3. Time from symptom onset to randomization ≤3 hours<br>4. NIHSS score 4-25 at baseline<br>5. Pre-stroke modified Rankin Scale score 0-1<br>6. Ability to provide informed consent (patient or legally authorized representative) | 1. Intracranial hemorrhage within the past 3 months (including intracerebral, intraventricular, subarachnoid, subdural, or epidural)<br>2. Severe hepatic dysfunction (ALT or AST >3 times upper limit of normal) or renal dysfunction (serum creatinine >3.0 mg/dl or GFR <30 ml/min/1.73m$^2$), or ongoing dialysis<br>3. Systolic blood pressure <90 mmHg or >220 mmHg<br>4. Bradycardia (heart rate <60 beats/min) or sick sinus syndrome<br>5. History of drug or food allergies, or known allergy to study drug components<br>6. Treatment with butylphthalide-containing medications after stroke onset<br>7. History of congenital or acquired hemorrhagic diseases, coagulation factor deficiencies, or thrombocytopenia<br>8. Pregnancy, breastfeeding, or planned pregnancy within 90 days<br>9. Severe mental disorders or dementia preventing informed consent or follow-up<br>10. Concurrent malignant tumors or severe systemic diseases with expected survival <90 days<br>11. Participation in other interventional clinical studies within 30 days prior to randomization or current participation in such studies<br>12. Any other condition deemed unsuitable for study participation by the investigator |

Figure 2. Inclusion and exclusion criteria for the BENEFIT trial

Abbreviation: ALT, alanine aminotransferase; AST, aspartate aminotransferase; NIHSS, National Institutes of Health stroke scale; GFR, glomerular filtration rate; mmHg, millimeters of mercury; bpm, beats per minute.

per 100 mL), manufactured by CSPC NBP Pharmaceutical Co., Ltd. Patients meeting the inclusion and exclusion criteria will be randomly assigned in a 1:1 ratio to the early initiation group (drug administration within 3 hours of stroke onset) or the late initiation group (drug administration between 3 and 6 hours of stroke onset). After obtaining informed consent and completing screening, investigators will assign randomization numbers and corresponding treatment groups using a randomization system. For patients in the early initiation group, NBP should be administered within 3 hours of stroke onset, with the initiation time recorded. For the late initiation group, NBP should be administered between 3 and 6 hours of stroke onset, with the initiation time documented. Both groups will receive NBP Injection at a dose of 100 mL per infusion, twice daily, for 12±2 consecutive days. The drug will be administered intravenously. All patients will receive standard care for acute ischemic stroke based on local guidelines and practices, including intravenous thrombolysis and/or endovascular thrombectomy if indicated and not contraindicated. All secondary prevention measures, including antithrombotic therapy and risk factor management, will follow guideline recommendations. However, neuroprotective medications such as human urinary kallikrein, edaravone, edaravone-dexborneol, and any ginkgo-containing injections are prohibited. Follow-up assessments will be conducted at baseline, 24±2 hours, 6±1 days, 12±2 days, and 90±7 days after randomization. Study outcomes will be evaluated by blinded assessors.

*Quality control and data management*

All study personnel will undergo standardized training on protocol procedures, outcome assessments, and data collection methods before study initiation. A detailed operations manual will be provided to ensure consistency across sites. Regular monitoring visits will be conducted to verify protocol adherence and data quality. The eCRF system will incorporate automated data checks and validation rules. An independent quality assurance team will perform periodic audits of study conduct and documentation.

Data security and confidentiality will be maintained through encrypted databases with restricted access. Regular data backups and verification procedures will be implemented. All study documents will be archived according to regulatory requirements.

*Sample size calculation*

This exploratory trial aims to recruit a sufficient number of participants to ensure that at least 200 patients are randomized. The sample size is based on feasibility considerations and the exploratory nature of the study, rather than formal power calculations. The total enrollment will be adjusted to account for potential protocol violations and follow-up losses.

*Outcome measures and assessment*

The primary outcome measure is the proportion of patients achieving a modified Rankin Scale (mRS) score of 0-2 at 90±7 days after randomization, assessed by independent evaluators blinded to treatment assignment. Secondary outcomes include the proportion of patients with mRS score 0-1 at 90±7 days, changes in NIHSS score and proportion achieving ≥4-point improvement at 6±1 and 12±2 days, early neurological deterioration (defined as any new neurological symptoms or worsening of pre-existing deficits meeting at least one of the following criteria: an increase of ≥2 points in total NIHSS score, ≥1 point in NIHSS consciousness score [items 1a-1c], ≥1 point in NIHSS motor score [items 5a-6b], or any new neurological deficit not assessed by the NIHSS) at 24±2 hours and 6±1 days, rates of futile recanalization (defined as achieving good recanalization after EVT, with angiographic evidence showing TICI 2b-3, mTICI 2c-3, or eTICI 2c-3 grades, but poor neurological functional outcomes with mRS ≥3 at 3 months), ischemic stroke recurrence, and composite vascular events at 90±7 days, infarct volume changes between baseline and 12±2 days (measured as low-density regions segmented on non-contrast CT using a machine learning algorithm validated by neuroimaging experts), and quality of life using EQ-5D score at 90±7 days.

Safety outcomes will be monitored throughout the study period, including rates of symptomatic intracranial hemorrhage at 24±2 hours and 6±1 days after randomization, vascular death (defined as death due to stroke, myocardial infarction, or other vascular causes) and all-cause mortality at 90±7 days, and investigator-reported adverse events. All outcomes will be evaluated according to standardized criteria by trained assessors who are blinded to treatment allocation, ensuring unbiased assessment of treatment effects between early and late NBP initiation groups.

*Clinical endpoint assessment and safety monitoring*

An independent Clinical Endpoint Committee (CEC) has been established for this study. The CEC consists of experienced neurologists not involved in the study, who are responsible for evaluating and adjudicating primary and secondary clinical endpoint events according to pre-defined criteria. All potential endpoint events will be reviewed by the CEC in a blinded manner to ensure consistency and objectivity in outcome assessment.

Given the scale and duration of this study, as well as the existing safety data on NBP, an independent Data and Safety Monitoring Board (DSMB) was not established. However, rigorous safety monitoring procedures will be implemented. The principal investigator will continuously monitor participant safety, regularly review adverse event reports, and take appropriate measures when necessary. In addition, study team members and independent safety experts will hold regular safety review meetings to evaluate potential safety concerns.

If any serious safety issues arise during the study, the research team will immediately assess the situation and consider suspending or terminating the study if warranted. All safety data will be promptly reported to relevant ethics committees and regulatory authorities.

*Statistical analyses*

This exploratory trial aims to enroll a sufficient number of participants to ensure that at least 200 patients are randomized. The total enrollment will be adjusted to account for an estimated proportion of participants who may not complete the study according to protocol or may be lost to follow-up. This approach, rather than a formal power calculation, is based on feasibility considerations and the exploratory nature of the study.

The analyses will be conducted on three populations: intention-to-treat (ITT) population (all randomized patients), per-protocol (PP) population (all randomized patients who complete the study without major protocol violations), and safety population (all patients who receive at least one dose of the study drug).

The primary endpoint analysis will follow the ITT principle. Missing values for the primary outcome will be imputed using the last observation carried forward (LOCF) method. We will use a modified poisson regression model with robust sandwich variance estimation to calculate the risk ratio (RR) and its 95% confidence interval (CI). Adjusted analyses will be performed using the inverse probability of treatment weighting (IPTW) approach. To assess the center effect, a generalized estimating equation (GEE) poisson model with a center clustering term will be used. Sensitivity analyses including PP analysis will be performed. Pre-specified subgroup analyses will also be conducted to assess the robustness of the results, based on the following baseline variables: age (≤60 years vs. >60 years), sex (male vs. female), stroke etiology and mechanism

(classified by the TOAST criteria), baseline NIHSS score (4–15 vs. ≥16), type of reperfusion therapy (intravenous thrombolysis, mechanical thrombectomy, or none), presence of hypertension (yes vs. no), hyperlipidaemia (yes vs. no) and diabetes (yes vs. no).

Secondary endpoints will be analyzed descriptively without formal statistical inference. Specifically, binary outcomes will be analyzed using modified Poisson regression, continuous outcomes using win ratio. Safety analyses will be based on the safety analysis set, using Cox proportional hazards models to estimate hazard ratios (HRs) and their 95% CIs for time-to-event outcomes. All adjusted analyses will be performed using the IPTW approach. No formal adjustment for multiplicity will be made for secondary endpoints, which should be interpreted as exploratory. No interim analyses for efficacy or futility are planned. Pre-specified covariates for adjusted analyses include age, baseline NIHSS score, time from symptom onset to randomization, mRS score prior to onset and the use of reperfusion therapies. However, if baseline characteristics show no significant differences as assessed by standardized mean differences (SMD), adjustment will not be performed. All analyses will be performed using R software (version 4.3.1). The findings from this study will provide important insights to inform future large-scale confirmatory trials.

## DISCUSSION

This protocol describes the BENEFIT trial design, which addresses a fundamental question in stroke neuroprotection: whether timing of administration influences treatment efficacy. This is particularly relevant given the historical challenges in translating promising neuroprotective agents from bench to bedside.[7] Previous clinical trials have demonstrated NBP's benefits in stroke patients[9,16,17], but the optimal therapeutic time window remains unclear.[9]

The trial's key strengths include its focus on early intervention, multicenter design, and standardized protocols.[18] The use of blinded outcome assessment minimizes bias.[19] The study innovatively applies the "time is brain" concept to neuroprotective interventions.[14,19]

We acknowledge several limitations. The open-label design may introduce bias[23], though mitigated by blinded outcome assessment. The study's conduct exclusively in Chinese centers may limit generalizability. The 90-day follow-up, while standard[24], may not capture longer-term outcomes.

If early NBP administration proves superior, this could fundamentally change acute stroke care protocols.[25] The biomarker analyses could enable more personalized approaches to neuroprotection. Future research should explore NBP's interaction with reperfusion therapies and potential therapeutic window extension through novel delivery methods.

In conclusion, the BENEFIT trial represents a significant step forward in stroke neuroprotection research. By addressing the critical question of timing, this study has the potential to optimize the use of NBP and inform future neuroprotective strategies.

## DISCLOSURE

Financial support: This study was supported by CSPC NBP Pharmaceutical Co., Ltd., which provided sponsorship for the trial. Additional funding was provided by the National Science & Technology Fundamental Resources Investigation Program of China to L.Z. (No. 2018FY100900), the Hunan Provincial Natural Science Foundation of China Grant to L.Z. (No. 2023JJ60144), the Central South University Research Programme of Advanced Interdisciplinary Projects in Changsha Studies to L.Z. (No. 2023QYJC011) and Y.Z. (No. 2021JJ30923), the Provincial Science and Technology Innovation Leading Talents Project to L.Z. (No. 2021RC4014), Major Science and Technology Projects in Changsha to L.Z. (No. kq2301008),the Hunan Provincial Health High-Level Talent Scientific Research Project to L.Z. (No. R2023069), the Major Basic Research Projects in Hunan Province to L.Z. (No. 2024JC0004), and the National Natural Science Foundation of China to L.Z. (No. 82471364).

Conflict of interest: None

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