Complete (*N* = 86)

Quit the test (*N* = 6)

Reasons:

* Death (*N* = 6)

Group B (*N* = 156)

Group A (*N* = 156)

PPS set: Group B (*N* = 93)

PPS set: Group A (*N* = 92)

Eliminate nonconformances (*N* = 64):

Reasons:

* 1. Unsatisfactory effect (*N* = 19)
* 2. Intolerable adverse events (*N* = 3)
* 3. Lost to follow-up (*N* = 12)
* 4. Subject withdrawal (*N* = 5)
* 5. Subjects have poor compliance (*N* = 10)
* 6. Use of prohibited drugs (*N* = 5)
* 7. Other (*N* = 10)

Eliminate nonconformances (N=63):

Reasons:

* 1. Unsatisfactory effect (*N* = 10)
* 2. Intolerable adverse events (*N* = 8)
* 3. Lost to follow-up (*N* = 18)
* 4. Subject withdrawal (*N* = 4)
* 5. Subjects have poor compliance (*N* = 11)
* 6. Use of prohibited drugs (*N* = 4)
* 7. Other (*N* = 8)

The treatment was double-blind (*N* = 312)

Screening (*N* = 312)

Screening of failure (*N* = 0)

Untreated (*N* = 0)

Randomization (*N* = 312)

Complete (*N* = 77)

Quit the test (*N* = 16)

Reasons:

* 1. Tracheotomy (*N* = 2)
* 2. Death (*N* = 13)
* 3. Fall off (*N* = 1)

**Supplementary Figure 1:** Study flow chart.

PPS：per protocol set

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**Supplementary Figure 2**: Changes in ALSFRS-R scores at different visits in the two groups (A: placebo group, B: NBP group). ALSFRS-R: Revised Amyotrophic Lateral Sclerosis Functional Rating Scale; NBP: DL-3-n-butylphthalide.



**Supplementary Figure 3:** Changes in MRC scores at different visits in the two groups (A: placebo group, B: NBP group). MRC: Medical Research Council; NBP: DL-3-n-butylphthalide.



**Supplementary Figure 4**: Changes in predicted percentages of FVC at different visits in the two groups (A: placebo group, B: NBP group). FVC: Forced vital capacity; NBP: DL-3-n-butylphthalide.



**Supplementary Figure 5**: Changes in CGI scores at different visits in the two groups (A: placebo group, B: NBP group). CGI: Clinical global impression; NBP: DL-3-n-butylphthalide.

**Supplementary Table 1: Baseline characteristics of patients with ALS in the two groups.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Clinical features** | **NBP (*n* = 93)** | **Placebo (*n* = 92)** |  | ***P*-value** |
| Gender ratio (M/F) | 61/32 | 70/22 | *χ*2=2.46  | 0.12 |
| Age at the first visit | 54.87 ± 10.39 | 52.80 ± 10.20 | *Z* = 1.35 | 0.18 |
| Duration from onset to presentation (day) | 11.90± 4.60 | 11.60 ± 4.30 | *Z* = 0.44 | 0.67 |
| Site of onset (upper/lower/both limb) | 38/10/45 | 37/10/45 | *χ*2 = 0.01 | 0.10 |
| Bulbar involved at the first visit (Y/N) | 37/56 | 34/58 | *χ*2 = 0.16 | 0.690 |
| BMI (kg/m2) | 23.84 ± 3.37 | 23.70 ± 3.41 | *Z* = 0.14 | 0.89 |
| ALS-FRS | 40.58 ± 3.88 | 40.49 ± 4.28 | *Z* = 0.06 | 0.95 |
| FVC | 95.36 ± 13.88 | 91.82 ± 15.01 | *Z* = 1.65 | 0.10 |
| Total MRC score  | 103.57 ± 11.44 | 101.34 ± 10.33 | *Z* = 1.90 | 0.06 |
| CGI 1 | 3.31 ± 0.86 | 3.49 ± 0.87 | *Z* = 1.28 | 0.20 |

ALS: Amyotrophic lateral sclerosis; ALSFRS-R: Revised Amyotrophic Lateral Sclerosis Functional Rating Scale; BMI: Body mass index; CGI: Clinical Global Impression; FVC: Forced vital capacity; MRC: Medical Research Council; NBP: DL-3-n-butylphthalide.

**Supplementary Table 2: Changes in ALSFRS-R scores between the two groups at different visits.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **ALSFRS-R # (n1/n2)** | **NBP (mean ± SD)** | **Placebo (mean ± SD)** |  | ***P*-value** |
| ALSFRS-R 1 (93/92) | 40.58 ± 3.88 | 40.49 ± 4.28 | *Z* = 0.06 | 0.95 |
| ALSFRS-R 2 (87/92) | 38.48 ± 5.28 | 37.63 ± 5.72 | *Z* = 0.98 | 0.33 |
| ALSFRS-R 3 (86/89) | 35.57 ± 6.58 | 34.35 ± 6.66 | *Z* = 1.25 | 0.21 |
| ALSFRS-R 4 (80/87) | 33.18 ± 8.24 | 31.28 ± 7.40 | *Z* = 1.71 | 0.09 |
| ALSFRS-R 5 (76/84) | 29.83 ± 9.13 | 28.55 ± 7.95 | *Z* = 0.90 | 0.37 |

ALSFRS-R: Revised Amyotrophic Lateral Sclerosis Functional Rating Scale; NBP: DL-3-n-butylphthalide; SD: Standard deviation.

ALSFRS-R 1: before treatment; ALSFRS-R 2: 3 months after treatment; ALSFRS-R 3: 6 months after treatment; ALSFRS-R 4: 9 months after treatment; ALSFRS-R5: 12 months after treatment; n1: Number of patients in the NBP group; n2: Number of patients in the placebo group.

**Supplementary Table 3: Differences in total MRC scores between the two groups at different visits.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Total MRC score # (n1/n2)** | **NBP (mean ± SD)** | **Placebo (mean ± SD)** |  | ***P*-value** |
| Total MRC score 1 (93/92) | 103.57 ± 11.44 | 101.34 ± 10.33 | *Z* = 1.90 | 0.06 |
| Total MRC score 2 (83/91) | 98.46 ± 14.87 | 95.92 ± 13.22 | *Z* = 1.56 | 0.12 |
| Total MRC score 3 (81/84) | 91.83 ± 17.9 | 87.81 ± 16.28 | *Z* = 1.72 | 0.08 |
| Total MRC score 4 (71/77) | 87.01 ± 19.92 | 80.51 ± 18.65 | *Z* = 2.16 | 0.03 |
| Total MRC score 5 (55/63) | 80.27 ± 22.10 | 77.25 ± 16.88 | *Z* = 0.88 | 0.38 |

MRC: Medical Research Council; NBP: DL-3-n-butylphthalide; SD: Standard deviation.

n1: Number of patients in the NBP group; n2: Number of patients in the placebo group; Total MRC score 1: Before treatment; Total MRC score 2: 3 months after treatment; Total MRC score 3: 6 months after treatment; Total MRC score 4: 9 months after treatment; Total MRC score 5: 12 months after treatment.

**Supplementary Table 4: Differences in predicted percentages of FVC between the two groups at different visits.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **%FVC # (n1/n2)** | **NBP (mean ± SD)** | **Placebo (mean ± SD)** |  | ***P*-value** |
| %FVC 1 (86/89) | 95.36 ± 13.88 | 91.82 ± 15.01 | *Z* = 1.65 | 0.10 |
| %FVC 2 (63/72) | 93.57 ± 15.10 | 86.61 ± 17.35 | *Z* = 2.65 | 0.01 |
| %FVC 3 (62/63) | 89.20 ± 18.96 | 79.98 ± 21.86 | *Z* = 2.83 | 0.01 |
| %FVC 4 (54/51) | 84.25 ± 17.57 | 79.69 ± 25.38 | *Z* = 1.20 | 0.23 |
| %FVC 5 (43/39) | 83.94 ± 18.99 | 77.08 ± 22.86 | *Z* = 1.52 | 0.13 |

FVC: Forced vital capacity; NBP: DL-3-n-butylphthalide; n1: Number of patients in the NBP group; n2: Number of patients in the placebo group; SD: Standard deviation.

%FVC: Percentage of predicted FVC; %FVC 1: Before treatment; %FVC 2: 3 months after treatment; %FVC 3: 6 months after treatment; %FVC 4: 9 months after treatment; %FVC 5: 12 months after treatment.

**Supplementary Table 5: Differences in CGI between the two groups at different visits.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **CGI # (n1/n2)** | **NBP (mean ± SD)** | **Placebo (mean ± SD)** |  | ***P*-value** |
| CGI 1(93/92) | 3.31 ± 0.86 | 3.49 ± 0.87 | *Z* = 1.28 | 0.20 |
| CGI 2 (84/91) | 3.65 ± 0.88 | 3.74 ± 0.80 | *Z* = 0.76 | 0.45 |
| CGI 3 (82/84) | 4.05 ± 0.93 | 4.13 ± 0.94 | *Z* = 0.34 | 0.73 |
| CGI 4 (75/78) | 4.37 ± 0.94 | 4.46 ± 1.00 | *Z* = 0.38 | 0.71 |
| CGI 5 (67/71) | 4.76 ± 1.10 | 4.76 ± 1.05 | *Z* = 0.06 | 0.95 |

NBP: DL-3-n-butylphthalide; SD: Standard deviation.

CGI: Self-administered Clinical Global Impression scale; CGI 1: Before treatment; CGI 2: 3 months after treatment; CGI 3: 6 months after treatment; CGI 4: 9 months after treatment; CGI 5: 12 months after treatment; n1: Number of patients in the NBP group; n2: Number of patients in the placebo group.

**Supplementary Table 6: Most common adverse events in the two groups.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Adverse event** | **NBP group (*n* = 93)** | **Placebo group (*n* = 92)** | ***P***-**value** |
| Diarrhea | 2 (2.15) | 2 (2.17) | 1.00 |
| Dry mouth | 2 (2.15) | 1 (1.09) | 1.00 |
| Lower limb edema | 2 (2.15) | 1 (1.09) | 1.00 |
| Dizzy | 2 (2.15) | 3 (3.26) | 0.99 |
| Cough | 1 (1.08) | 2 (2.17) | 0.99 |
| Oropharyngeal pain | 1 (1.08) | 2 (2.17) | 0.99 |
| rash | 1 (1.08) | 3 (3.26) | 0.61 |
| ALT elevated | 18 (19.35) | 11 (11.96) | 0.17 |
| AST elevated | 4 (4.30) | 7 (7.61) | 0.34 |
| CK elevated | 14 (15.05) | 17 (18.48) | 0.53 |

ALT: Alanine transaminase; AST: Aspartate transaminase; CK: Creatine kinase; NBP: DL-3-n-butylphthalide.

Data were presented as *n* (%).