γ-Linolenic Acid versus α-Lipoic Acid for Treating Painful Diabetic Neuropathy in Adults: A 12-Week, Double-Placebo, Randomized, Noninferiority Trial

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Background: This study was a multicenter, parallel-group, double-blind, double-dummy, randomized, noninferiority trial to evaluate the efficacy and safety of γ-linolenic acid (GLA) relative to α-lipoic acid (ALA) over a 12-week treatment period in type 2 diabetes mellitus (T2DM) patients with painful diabetic peripheral neuropathy (DPN).

Methods: This study included 100 T2DM patients between 20 and 75 years of age who had painful DPN and received either GLA (320 mg/day) and placebo or ALA (600 mg/day) and placebo for 12 weeks. The primary outcome measures were mean changes in pain intensities as measured by the visual analogue scale (VAS) and the total symptom scores (TSS).

Results: Of the 100 subjects who initially participated in the study, 73 completed the 12-week treatment period. Per-protocol analyses revealed significant decreases in the mean VAS and TSS scores compared to baseline in both groups, but there were no significant differences between the groups. The treatment difference for the VAS (95% confidence interval [CI]) between the two groups was −0.65 (−1.526 to 0.213) and the upper bound of the 95% CI did not exceed the predefined noninferiority margin (δ1=0.51). For the TSS, the treatment difference was −0.05 (−1.211 to 1.101) but the upper bound of the 95% CI crossed the noninferiority margin (δ2=0.054). There were no serious adverse events associated with the treatments.

Conclusion: GLA treatment in patients with painful DPN was noninferior to ALA in terms of reducing pain intensity measured by the VAS over 12 weeks.

Keywords: Diabetic neuropathies; Gamma-linolenic acid; Thiocic acid

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INTRODUCTION

The occurrence of type 2 diabetes mellitus (T2DM) is increasing worldwide [1], and in Korea, one in every seven adults aged 30 years or older has diabetes [2]. Diabetic sensorimotor distal symmetric polyneuropathy, or diabetic peripheral neuropathy (DPN), is the most common neuropathy associated with diabetes as well as the most common complication in diabetes patients. Approximately one in every three T2DM patients in Korea has DPN [3], and 42.3% of those with DPN experience painful symptoms or are taking medication(s) for their current pain [4]. Although many available guidelines recommend anticonvulsants and antidepressants as first-line treatments for painful DPN, there are unmet needs in terms of efficacy and tolerability, and these treatment modalities modulate the pain rather than favorably influencing the underlying neuropathic processes [5]. Additionally, the painful symptoms of DPN may vary with the course of nerve damage, the presence of comorbidities, and/or ethnic and cultural differences [6], which creates therapeutic challenges regarding the management of painful symptoms [5].

A novel treatment option, γ-linolenic acid (GLA), is an n-6 polyunsaturated fatty acid that is converted from dietary linolenic acid (primrose oil), and as an essential component of structural phospholipids in neural cell membranes, is necessary for the maintenance of normal nerve membrane structure and function [7]. For example, decreases in the production and increases in the destruction of GLA are associated with impaired nerve conduction in patients with T2DM [8,9]. Thus, based on the pathogenetic mechanisms of DPN, GLA has been developed as a potential disease-modifying therapeutic drug [10,11], along with other potential treatment modalities such as α-lipoic acid (ALA) [12,13], aldose reductase inhibitors [14], vascular endothelial growth factors [15], and protein kinase C-β inhibitors [16]. These treatment options were designed to favorably influence the underlying pathophysiology of DPN rather than merely provide symptomatic relief for DPN patients. GLA treatment corrects impaired nerve function in animal models of diabetes [17] and is beneficial for neurophysiological parameters, thermal thresholds, and clinical sensory symptoms in patients with T2DM [8]. A previous study of 934 Korean patients with painful DPN found that 40.2% (n = 396) were prescribed ALA and 17.2% (n = 169) were prescribed GLA [3]. Although the efficacies of oral and intravenous ALA have been established by meta-analyses of clinical trials [18,19], the efficacy of GLA for improving the symptoms of patients with painful DPN has yet to be determined.

Thus, the primary aim of the present study was to investigate the noninferiority of the efficacy of GLA (Evoprim; Dalim Biotech, Seoul, Korea) relative to ALA (Lipo-A HR; Dalim Biotech) as an active comparator. GLA was orally administered for 12 weeks as a treatment for the neuropathic symptoms of T2DM patients with painful DPN.

METHODS

Study population

Subjects were eligible for the present study if they agreed to participate, were between 20 and 75 years of age, had T2DM with glycosylated hemoglobin (HbA1c) levels ≤11.0% at the time of screening, had an average visual analogue scale (VAS) score ≥4.0 for the 24-hour average pain score (0 to 10 numerical rating scale), and a diagnosis of DPN after a thorough evaluation for other causes of neuropathy at the screening. The exclusion criteria consisted of the following: a confounding neurological disease or neuropathy caused by progressive or degenerative disorders that may have interfered with the assessment of DPN severity; uncontrolled hypertension (systolic or diastolic blood pressure levels ≥160 or ≤100 mm Hg or ≥95 or ≤60 mm Hg, respectively); an amputated foot or leg; a clinically significant cardiac, pulmonary, gastrointestinal, hematological, or other endocrinological disease (e.g., abnormal thyroid function test even though taking medication); organ transplants; aspartate aminotransferase or alanine aminotransferase levels >3 times normal levels; serum creatinine levels >2.0 mg/dL; drug or alcohol abuse within the last year; use of an investigational drug within the last 6 months; severe or anaphylactic reactions; pregnant or lactating women; and/or corticosteroid or local anesthetic therapies within the last 2 months. Subjects were enrolled at 11 sites in the Republic of Korea and the study was carried out from January 26, 2016 to July 25, 2018 (ClinicalTrials.gov number, #NCT03914404). All study procedures were conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice, and were approved by Institutional Review Board at all sites (IRB No.: CUH 2015-06-001, XCI15SMV0063K, 1528, GAIRB2015-237, XCI15SMV0063S, D-1506-022-041, CR-15-069-L, 110757-201507-HR-01, SCHCA 2015-06-021-007, 4-2015-0628, SGPAIK 2017-08-01). Written informed consent was obtained from all patients.
Study design and medication

**Study design**
The present study was a multicenter, double-blind, double-dummy, randomized, active-controlled, noninferiority trial that compared GLA (twice daily) and placebo (once daily) to ALA (once daily) and placebo (twice daily) to investigate changes in VAS and total symptom scores (TSS) between baseline and the end of the 12-week study period (Supplementary Fig. 1). All subjects engaged in a wash-out period for 2 weeks during which all current medications for the treatment of DPN (anticonvulsants, tricyclic antidepressants, serotonin–norepinephrine reuptake inhibitors, norepinephrine reuptake inhibitors, tramadol, opioids, steroids, topical analgesics containing lidocaine or capsaicin, and other prohibited medications) were discontinued. Both placebos used in this trial were prescribed twice daily to all subjects during the wash-out period. Subsequently, eligible subjects were randomly assigned to receive the following treatments twice daily over 12 consecutive weeks: GLA and placebo or ALA and placebo.

At the randomization visit after the 2-week wash-out period, the subjects were required to have a VAS score ≥4.0. A total of 124 patients were scheduled for randomization into two groups. Site investigators responsible for obtaining and analyzing data for the primary and secondary outcomes were blinded to the patient randomization procedure. Due to the nature of the study, all subjects and clinical staff were also blinded to the study group assignments. A treatment duration of 12 weeks was selected because there is a significant increase in the levels of plasma GLA and its metabolite dihomo-γ-linolenic acid (DGLA) after 4 weeks of treatment [20]. Additionally, a plateau in the TSS response is observed after 5 weeks of oral ALA treatment, which has a slower onset of efficacy [21].

**Study medication**
The study medication (Evoprim, 735 mg soft capsules; Dalim Biotech) contained 450 mg of evening primrose oil, which corresponds to 40 mg of GLA per capsule; the dosages consisted of four capsules taken twice daily (320 mg/day of GLA) 30 minutes before breakfast and dinner. The active control medication was 600 mg/day of ALA (Lipo-A HR, 828 mg tablets; Dalim Biotech); the dosage consisted of one tablet taken once daily 30 minutes before breakfast. The placebo capsules and tablets for GLA and ALA were identical in appearance to the Evoprim capsules and Lipo-A HR tablets, respectively. Treatment duration was 12 weeks and treatment compliance was defined as the intake of at least 80% of the trial medications. No other agents for the treatment of DPN were allowed, but all subjects were advised to continue medication with any anti-diabetic drug or drug for managing hypertension or dyslipidemia during the study period.

Assessment of diabetic neuropathy
At the screening visit, all subjects were evaluated for DPN with the Michigan Neuropathy Screening Instrument questionnaire (MNSIQ) and physical examination (MNSIE) as well as the current perception threshold (CPT) test, which was measured using a Neurometer CPT device (Neurotron Inc., Baltimore, MD, USA). After completion of the MNSIQ, trained technicians examined the subjects for deformities, dry skin, callus, infections, ulcerations, vibration senses on the interphalangeal joints of both great toes, muscle strength reflexes using a hammer at the Achilles tendon on both ankles, and the monofilament test at the dorsum of both great toes [22]. The CPT was assessed as previously described [23]. Briefly, small electrodes were taped to the test sites (index fingers and great toes) and the responses to three different stimuli (2,000, 250, and 5 Hz) were recorded with increasing currents at each frequency.

Diagnosis of DPN
DPN was diagnosed based on the presence of either of the following criteria: (1) an MNSIE score ≥2 or (2) symptoms of pain, burning, tingling, and/or loss of sensation and abnormal CPT results of the peroneal nerve at any frequency (reference ranges: 2.0 to 5.26 mA at 2,000 Hz, 0.62 to 2.11 mA at 250 Hz, and 0.3 to 1.73 mA at 5 Hz) [24]. These criteria are based on the recommendations of the Toronto Diabetic Neuropathy Expert Group [25].

Assessment of outcomes and safety

**Primary outcome measures**
The primary outcome measures included scores on the VAS and TSS, which were assessed as previously described [4,21]. The VAS and TSS scores were measured at screening, at baseline prior to the initiation of the study treatment, and after 4 and 12 weeks of treatment. The VAS is an 11-point numeric rating scale ranging from 0 to 10 (0=no pain and 10=the worst pain imaginable) that is based on the most recent 24-hour average experience of pain. The TSS is a summation of symptom scores for stabbing pain, burning pain, paresthesia, and numbness by frequency (occasionally, often, or continuous) and in-
tensity (not present, mild, moderate, or severe) on which scores range from 0 to 14.64.

Secondary outcome measures
The MNSIQ and MNSIE scores, CPT test, modified Brief Pain Inventory for DPN (mBPI-DPN), and EuroQol-5 dimensions (EQ 5D) were conducted as previously described [4,22]. All neurological assessments were performed by trained investigators under supervision of the study physician, who was a certified endocrinologist with the medical board of internal medicine.

Safety analyses
Safety measures included the frequencies of treatment-emergent adverse drug reactions (TEADRs) and the monitoring of serious adverse events (SAEs) or other signs, including systolic and diastolic blood pressure levels, heart rate after 5 minutes of sitting at rest, body weight, and standard laboratory parameters; each of these variables was measured at the beginning and end of the study. Adverse events were monitored throughout the entire study, TEADRs were determined by study investigators, and SAEs were defined by the protocol.

Laboratory assays
At each study site, blood samples were collected from the subjects following a 12-hour overnight fast via punctures of the forearm vein, and laboratory measurements were performed immediately after centrifugation and clotting. At each site, fasting serum glucose, creatinine, and lipid levels were measured using kits according to the manufacturer’s instructions. Low density lipoprotein cholesterol (LDL-C) levels were calculated using the Friedewald formula [26] and HbA1c levels were measured using high-performance liquid chromatography; all measurements were performed at baseline and at the final visit.

Sample size calculation
The sample size calculation was based on the primary efficacy variable (i.e., TSS scores) and the noninferiority of the GLA treatment group compared to the ALA treatment group. Based on the assumptions that the difference of the GLA treatment group was 3.776, the difference of the ALA treatment group was 2.7, and the common standard deviation (SD) was 1.76 with a noninferiority margin of $\delta_1=0.054$, 60 patients per group would have had a statistical power of 80% to confirm noninferiority using a two-sided significance level of $P<0.05$. The noninferiority margin was estimated based on a previous trial of ALA in Korea [27].

Statistical analysis
All randomized subjects that received at least one of the investigation products were included in the present analyses. Additionally, analyses based on the per-protocol (PP) set were performed to examine the robustness of the efficacy outcomes analysis; subjects who had major protocol deviations such as noncompliance with the study drug or the use of a prohibited medication were excluded from the PP analysis. Analyses based on the intent-to-treat set were performed to examine the degrees of robustness of the demographic information and the safety analysis. Independent $t$-tests for mean changes in values between the GLA and ALA groups and paired $t$-tests for changes between the baseline and 12-week assessments within each group were conducted to assess the efficacy outcomes and safety factors. Categorical variables, including demographic information and adverse events, were evaluated with chi-squared tests or Fisher’s exact tests. Additionally, 95% confidence intervals (CI) for treatment differences on the VAS and TSS (GLA-ALA) at week 12 were estimated; if the upper bounds of the 95% CI did not exceed the predefined noninferiority margins ($\delta_1=0.51$ and $\delta_2=0.054$, respectively), it was concluded that GLA was not inferior to ALA. All statistical analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC, USA).

RESULTS
The subject distribution throughout the trial is shown in Supplementary Fig. 2 [28]. Of the 124 subjects that were initially screened for this study, 24 were ineligible for randomization; three patients did not meet the inclusion criteria, seven met the exclusion criteria, and 14 withdrew their consent. Thus, a total of 100 subjects entered the run-in phase. Of the 100 subjects who were randomly assigned to a group, 73 completed the trial and 27 (27%) discontinued participation during the treatment period. Of these 27 subjects, eight were withheld from the study due to the inclusion/exclusion criteria, and 14 withdrew consent. Thus, a total of 100 subjects entered the run-in phase. Of the 100 subjects who were randomly assigned to a group, 73 completed the trial and 27 (27%) discontinued participation during the treatment period. Of these 27 subjects, eight were withheld from the study due to the inclusion/exclusion criteria, seven withdrew consent, five did not comply with the treatment, five were taking prohibited medications during the trial period, one discontinued participation due to a dosing error, and one discontinued participation due to adverse events (Supplementary Fig. 2).
Primary outcomes
The demographic and clinical characteristics of the subjects are shown in Table 1. There were no significant differences between the groups in any of the baseline parameters or the mean VAS and TSS scores at baseline (total scores and individual sub-scores) (Table 2). The outcomes were analyzed using a PP approach; i.e., only data from patients who continued with the randomized treatment were considered for the present analyses [29].

After the 12-week treatment period, there were significant reductions in the mean VAS score of each group compared to baseline (all $P<0.001$) but the scores of the two groups did not significantly differ from each other ($P=0.137$) (Table 3). In the GLA group, the mean VAS score at baseline was 5.26±1.17, compared to 2.94±1.71 after 12 weeks of treatment. In the ALA group, the mean VAS score at baseline was 5.58±1.35, compared to 3.92±2.12 after 12 weeks of treatment. The differ-

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>GLA (n=48)</th>
<th>ALA (n=52)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>29 (60.4)</td>
<td>26 (50.0)</td>
<td>0.296</td>
</tr>
<tr>
<td>Age, yr</td>
<td>60.35±9.03</td>
<td>60.96±8.94</td>
<td>0.736</td>
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<tr>
<td>Duration of diabetes, yr*</td>
<td>9.63±8.16</td>
<td>12.81±8.92</td>
<td>0.066</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.02±3.19</td>
<td>25.26±3.71</td>
<td>0.729</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>126.69±12.65</td>
<td>128.94±9.82</td>
<td>0.320</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>75.63±8.32</td>
<td>75.37±7.08</td>
<td>0.867</td>
</tr>
<tr>
<td>FPG, mg/dL</td>
<td>129.71±30.52</td>
<td>134.71±46.92</td>
<td>0.526</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>6.96±0.88</td>
<td>7.25±1.17</td>
<td>0.169</td>
</tr>
<tr>
<td>BUN, mg/dL</td>
<td>15.68±4.41</td>
<td>16.26±6.38</td>
<td>0.593</td>
</tr>
<tr>
<td>S-Cr, mg/dL</td>
<td>0.84±0.21</td>
<td>0.83±0.22</td>
<td>0.882</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>146.50±27.23</td>
<td>158.90±35.57</td>
<td>0.055</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>137.02±75.97</td>
<td>153.21±104.71</td>
<td>0.376</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>49.67±12.14</td>
<td>51.83±14.24</td>
<td>0.418</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>69.52±27.84</td>
<td>77.34±30.17</td>
<td>0.182</td>
</tr>
<tr>
<td>Statin</td>
<td>33 (68.75)</td>
<td>39 (75.00)</td>
<td>0.487</td>
</tr>
<tr>
<td>OHA</td>
<td>44 (91.67)</td>
<td>51 (98.08)</td>
<td>0.192</td>
</tr>
<tr>
<td>OHA+Insulin</td>
<td>6 (12.50)</td>
<td>12 (23.08)</td>
<td>0.169</td>
</tr>
<tr>
<td>Insulin</td>
<td>8 (16.67)</td>
<td>13 (25.00)</td>
<td>0.307</td>
</tr>
</tbody>
</table>

Values are presented as number (%) or mean±standard deviation.

GLA, γ-linolenic acid; ALA, α-lipoic acid; BMI, body mass index; BP, blood pressure; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; BUN, blood urea nitrogen; S-Cr, serum creatinine; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; OHA, oral hypoglycemic agent.

*Duration of diabetes is from the time of diagnosis.

Table 2. Baseline primary and secondary outcome measures

<table>
<thead>
<tr>
<th>Variable</th>
<th>GLA (n=48)</th>
<th>ALA (n=52)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS score</td>
<td>5.25±1.19</td>
<td>5.62±1.33</td>
<td>0.153</td>
</tr>
<tr>
<td>Total TSS</td>
<td>4.25±2.36</td>
<td>5.12±3.25</td>
<td>0.881</td>
</tr>
<tr>
<td>Stabbing pain</td>
<td>1.64±1.07</td>
<td>1.67±1.17</td>
<td>0.555</td>
</tr>
<tr>
<td>Burning pain</td>
<td>1.14±1.00</td>
<td>1.27±1.18</td>
<td>0.117</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>0.78±1.08</td>
<td>1.15±1.27</td>
<td>0.114</td>
</tr>
<tr>
<td>Numbness</td>
<td>0.69±0.86</td>
<td>1.02±1.20</td>
<td>0.127</td>
</tr>
<tr>
<td>Michigan Neuropathy Screening Instrument</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Questionnaire</td>
<td>5.25±1.86</td>
<td>5.81±1.99</td>
<td>0.152</td>
</tr>
<tr>
<td>Physical examination</td>
<td>3.47±1.31</td>
<td>3.73±1.13</td>
<td>0.287</td>
</tr>
<tr>
<td>Current perception threshold, mA*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,000 Hz in left</td>
<td>4.38±2.11</td>
<td>3.88±1.70</td>
<td>0.193</td>
</tr>
<tr>
<td>2,000 Hz in right</td>
<td>4.08±1.82</td>
<td>3.66±1.71</td>
<td>0.241</td>
</tr>
<tr>
<td>250 Hz in left</td>
<td>2.11±1.91</td>
<td>2.13±2.32</td>
<td>0.968</td>
</tr>
<tr>
<td>250 Hz in right</td>
<td>1.97±1.76</td>
<td>1.75±1.40</td>
<td>0.488</td>
</tr>
<tr>
<td>5 Hz in left</td>
<td>1.54±1.98</td>
<td>1.60±2.38</td>
<td>0.894</td>
</tr>
<tr>
<td>5 Hz in right</td>
<td>1.55±1.92</td>
<td>1.16±1.17</td>
<td>0.230</td>
</tr>
<tr>
<td>Modified BPI-DPN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of total pain sites</td>
<td>2.77±1.48</td>
<td>2.73±1.29</td>
<td>0.885</td>
</tr>
<tr>
<td>Treatment of pain</td>
<td>0.52±0.50</td>
<td>0.42±0.50</td>
<td>0.333</td>
</tr>
<tr>
<td>Pain medication</td>
<td>0.50±0.51</td>
<td>0.44±0.50</td>
<td>0.568</td>
</tr>
<tr>
<td>Pain severity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worst</td>
<td>5.92±1.61</td>
<td>6.17±2.06</td>
<td>0.491</td>
</tr>
<tr>
<td>Least</td>
<td>2.58±1.51</td>
<td>2.83±1.83</td>
<td>0.473</td>
</tr>
<tr>
<td>Average</td>
<td>4.94±1.42</td>
<td>5.27±1.75</td>
<td>0.303</td>
</tr>
<tr>
<td>Now</td>
<td>3.42±2.28</td>
<td>3.96±2.52</td>
<td>0.261</td>
</tr>
<tr>
<td>Pain interference</td>
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<tr>
<td>General activity</td>
<td>3.23±2.58</td>
<td>3.71±2.99</td>
<td>0.391</td>
</tr>
<tr>
<td>Mood</td>
<td>3.92±2.66</td>
<td>4.58±2.74</td>
<td>0.225</td>
</tr>
<tr>
<td>Walking ability</td>
<td>2.69±2.59</td>
<td>3.58±3.03</td>
<td>0.119</td>
</tr>
<tr>
<td>Normal work</td>
<td>2.69±2.51</td>
<td>3.48±2.96</td>
<td>0.153</td>
</tr>
<tr>
<td>Relations with other people</td>
<td>2.15±2.37</td>
<td>2.65±2.72</td>
<td>0.324</td>
</tr>
<tr>
<td>Sleep</td>
<td>4.06±2.81</td>
<td>3.90±2.94</td>
<td>0.784</td>
</tr>
<tr>
<td>Enjoyment of life</td>
<td>3.19±2.65</td>
<td>3.25±2.89</td>
<td>0.911</td>
</tr>
<tr>
<td>EuroQol-5 dimensions</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>0.81±0.11</td>
<td>0.77±0.13</td>
<td>0.072</td>
</tr>
</tbody>
</table>

Values are presented as number (%) or mean±standard deviation.

GLA, γ-linolenic acid; ALA, α-lipoic acid; VAS, visual analogue scale; TSS, total symptom score; BPI, brief pain inventory; DPN, diabetic peripheral neuropathy.

*Peroneal nerve, lower leg.
γ-Linolenic acid in painful DPN

Table 3. Changes in primary outcomes from baseline to week 12

<table>
<thead>
<tr>
<th>Variable</th>
<th>GLA (n=35)</th>
<th>ALA (n=38)</th>
<th>Treatment difference (95% CI)</th>
<th>P value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Week 12</td>
<td>Difference</td>
<td>P value</td>
</tr>
<tr>
<td>VAS score</td>
<td>5.26±1.17</td>
<td>2.94±1.71</td>
<td>−2.31±1.92</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total score</td>
<td>3.86±2.12</td>
<td>2.18±2.12</td>
<td>−1.68±2.39</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stabbing pain</td>
<td>1.64±1.03</td>
<td>0.76±0.72</td>
<td>−0.88±1.18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Burning pain</td>
<td>1.12±1.02</td>
<td>0.79±0.84</td>
<td>−0.33±1.07</td>
<td>0.075</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>0.53±0.86</td>
<td>0.29±0.61</td>
<td>−0.24±1.00</td>
<td>0.167</td>
</tr>
<tr>
<td>Numbness</td>
<td>0.57±0.81</td>
<td>0.33±0.80</td>
<td>−0.24±0.79</td>
<td>0.083</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation.

GLA, γ-linolenic acid; ALA, α-lipoic acid; CI, confidence interval; VAS, visual analogue scale; TSS, total symptom score.

*<sup>a</sup>Analized by paired t-tests between baseline and week 12 in each group, ^<sup>b</sup>analyzed by independent t-tests assessing changes in values between the groups.

ences in the least-squares mean ± SD of the VAS score after 12 weeks of treatment were −2.31±1.92 in the GLA group and −1.66±1.81 in the ALA group. The treatment difference between the two groups was −0.65 (95% CI, −1.526 to 0.213), and therefore, the upper bound of the 95% CI did not exceed the predefined noninferiority margin (δ<sub>1</sub>=0.51), which suggests the noninferiority of GLA compared to ALA in terms of the VAS score.

There were also significant reductions in the mean total TSS scores in both groups. In the GLA group, the mean total TSS scores significantly decreased from 3.86±2.12 at baseline to 2.18±2.12 after 12 weeks of treatment (P<0.001). In the ALA group, the mean total TSS scores significantly decreased from 5.15±3.57 at baseline to 3.52±3.39 after 12 weeks of treatment (P<0.001). The differences in the least-squares mean of the total TSS score after 12 weeks of treatment were −1.66±2.39 in the GLA group and −1.63±2.55 in the ALA group, but the difference in changes on the TSS was not significant between the two groups (P=0.875). The treatment difference between the two groups was −0.65 (95% CI, −1.526 to 1.01), and therefore, the upper bound of the 95% CI crossed the noninferiority margin (δ<sub>1</sub>=0.545), which suggests that treatment with GLA did not satisfy the criteria for noninferiority compared to treatment with ALA in terms of the TSS. After 12 weeks of treatment, the TSS sub-scores for stabbing pain exhibited significant reductions in both groups (both P<0.001), whereas only the ALA group showed significant reductions in the sub-scores for paresthesia (P=0.167 for GLA, P=0.002 for ALA) and numbness (P=0.083 for GLA, P=0.017 for ALA) compared to baseline. The changes in the sub-scores for burning pain were not significant in either group (P=0.075 for GLA, P=0.436 for ALA) (Table 3). A response analysis after 12 weeks of treatment revealed that the percentages of clinical responders (a decrease in VAS or TSS score ≥40%) were 60.0% in the GLA group and 42.1% in the ALA group for the TSS; there were no significant differences between the two groups (χ<sup>2</sup>, P=0.127 and P=0.192, respectively).

Secondary outcomes

The mean levels of the subjects on the MNSIQ and MNSIE, all CPT measures, scores on the mBPI-DPN and EQ 5D at baseline, and scores on the mBPI-DPN and EQ 5D after 12 weeks of treatment are provided in Table 4. There were no significant differences between the two groups at baseline. The changes in the sub-scores for burning pain were not significant in either group (P=0.075 for GLA, P=0.436 for ALA) (Table 3). A response analysis after 12 weeks of treatment revealed that the percentages of clinical responders (a decrease in VAS or TSS score ≥40%) were 60.0% in the GLA group and 42.1% in the ALA group for the TSS; there were no significant differences between the two groups (χ<sup>2</sup>, P=0.127 and P=0.192, respectively).
Table 4. Changes in secondary outcomes from baseline to week 12

<table>
<thead>
<tr>
<th>Variable</th>
<th>GLA (n=35)</th>
<th>ALA (n=38)</th>
<th>Treatment difference (95% CI)</th>
<th>P value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Week 12</td>
<td>Difference</td>
<td>P value&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Michigan Neuropathy Screening Instrument</td>
<td>5.14±1.91</td>
<td>4.34±1.94</td>
<td>−0.80±2.01</td>
<td>0.025</td>
</tr>
<tr>
<td></td>
<td>5.71±2.07</td>
<td>5.13±2.37</td>
<td>−0.58±1.48</td>
<td>0.021</td>
</tr>
<tr>
<td>Physical examination</td>
<td>3.33±1.27</td>
<td>2.41±1.67</td>
<td>−0.91±1.14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>3.87±1.11</td>
<td>2.76±1.62</td>
<td>−1.11±1.28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current perception threshold, mA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,000 Hz in left</td>
<td>4.54±2.28</td>
<td>3.76±2.05</td>
<td>−0.78±1.93</td>
<td>0.023</td>
</tr>
<tr>
<td></td>
<td>3.80±1.88</td>
<td>3.67±1.60</td>
<td>−0.03±1.41</td>
<td>0.260</td>
</tr>
<tr>
<td>2,000 Hz in right</td>
<td>4.13±1.89</td>
<td>3.96±2.03</td>
<td>−0.16±1.64</td>
<td>0.556</td>
</tr>
<tr>
<td></td>
<td>3.61±1.81</td>
<td>3.67±2.08</td>
<td>0.06±1.07</td>
<td>0.751</td>
</tr>
<tr>
<td>250 Hz in left</td>
<td>2.27±2.15</td>
<td>1.74±1.19</td>
<td>−0.53±2.22</td>
<td>0.167</td>
</tr>
<tr>
<td></td>
<td>2.06±2.32</td>
<td>1.86±1.69</td>
<td>−0.20±1.51</td>
<td>0.425</td>
</tr>
<tr>
<td>250 Hz in right</td>
<td>2.13±1.99</td>
<td>2.08±1.82</td>
<td>−0.04±1.73</td>
<td>0.889</td>
</tr>
<tr>
<td></td>
<td>1.70±1.42</td>
<td>1.94±2.24</td>
<td>0.24±1.82</td>
<td>0.430</td>
</tr>
<tr>
<td>5 Hz in left</td>
<td>1.64±2.24</td>
<td>1.15±0.98</td>
<td>−0.49±2.15</td>
<td>0.183</td>
</tr>
<tr>
<td></td>
<td>1.54±2.36</td>
<td>1.31±1.73</td>
<td>−0.24±1.66</td>
<td>0.385</td>
</tr>
<tr>
<td>5 Hz in right</td>
<td>1.68±2.16</td>
<td>1.55±1.93</td>
<td>−0.12±1.94</td>
<td>0.707</td>
</tr>
<tr>
<td></td>
<td>1.12±1.06</td>
<td>1.37±2.14</td>
<td>0.24±1.86</td>
<td>0.427</td>
</tr>
<tr>
<td>Modified BPI-DPN</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of total pain sites</td>
<td>2.57±1.09</td>
<td>1.97±1.07</td>
<td>−0.60±1.14</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>2.68±1.25</td>
<td>2.45±1.95</td>
<td>−0.24±1.87</td>
<td>0.439</td>
</tr>
<tr>
<td>Treatment of pain</td>
<td>0.54±0.51</td>
<td>1.00±0.00</td>
<td>0.46±0.51</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>0.42±0.50</td>
<td>1.00±0.00</td>
<td>0.58±0.50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pain medication</td>
<td>0.51±0.51</td>
<td>1.00±0.00</td>
<td>0.49±0.51</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>0.45±0.50</td>
<td>1.00±0.00</td>
<td>0.55±0.50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pain severity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worst</td>
<td>5.94±1.71</td>
<td>3.74±2.47</td>
<td>−2.20±2.76</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>6.13±2.16</td>
<td>4.89±2.42</td>
<td>−1.24±2.10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Least</td>
<td>2.49±1.42</td>
<td>1.54±1.56</td>
<td>−0.94±1.57</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>2.82±1.92</td>
<td>2.26±1.91</td>
<td>−0.55±1.77</td>
<td>0.061</td>
</tr>
<tr>
<td>Average</td>
<td>4.83±1.42</td>
<td>3.03±1.71</td>
<td>−1.80±2.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>5.21±1.86</td>
<td>4.16±2.19</td>
<td>−1.05±1.82</td>
<td>0.001</td>
</tr>
<tr>
<td>Now</td>
<td>3.34±2.29</td>
<td>2.34±2.10</td>
<td>−1.00±2.53</td>
<td>0.026</td>
</tr>
<tr>
<td></td>
<td>3.95±2.50</td>
<td>2.87±2.21</td>
<td>−1.08±2.12</td>
<td>0.003</td>
</tr>
<tr>
<td>Pain interference</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General activity</td>
<td>3.43±2.74</td>
<td>1.74±2.05</td>
<td>−1.69±2.65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>3.87±3.09</td>
<td>3.24±2.81</td>
<td>−0.63±2.40</td>
<td>0.113</td>
</tr>
<tr>
<td>Mood</td>
<td>4.00±2.79</td>
<td>2.00±2.24</td>
<td>−2.00±2.91</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>4.71±2.78</td>
<td>3.50±2.51</td>
<td>−1.21±2.45</td>
<td>0.004</td>
</tr>
<tr>
<td>Walking ability</td>
<td>2.69±2.55</td>
<td>1.54±1.98</td>
<td>−1.14±2.64</td>
<td>0.015</td>
</tr>
<tr>
<td></td>
<td>3.39±3.00</td>
<td>2.74±2.95</td>
<td>−0.66±2.07</td>
<td>0.058</td>
</tr>
<tr>
<td>Normal work</td>
<td>2.74±2.48</td>
<td>1.51±1.95</td>
<td>−1.23±2.12</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>3.61±3.13</td>
<td>2.61±2.49</td>
<td>−1.00±2.45</td>
<td>0.016</td>
</tr>
<tr>
<td>Relations with other people</td>
<td>2.17±2.49</td>
<td>1.14±1.57</td>
<td>−1.03±2.37</td>
<td>0.015</td>
</tr>
<tr>
<td></td>
<td>2.87±2.92</td>
<td>1.87±2.20</td>
<td>−1.00±1.92</td>
<td>0.003</td>
</tr>
<tr>
<td>Sleep</td>
<td>4.23±2.82</td>
<td>2.00±2.06</td>
<td>−2.23±2.28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>3.97±3.04</td>
<td>2.74±2.56</td>
<td>−1.24±2.15</td>
<td>0.001</td>
</tr>
<tr>
<td>Enjoyment of life</td>
<td>3.11±2.54</td>
<td>1.37±2.00</td>
<td>−1.74±2.69</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>3.42±2.97</td>
<td>2.18±2.08</td>
<td>−1.24±2.69</td>
<td>0.007</td>
</tr>
<tr>
<td>EuroQol-5 dimensions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>0.81±0.09</td>
<td>0.85±0.16</td>
<td>0.04±0.15</td>
<td>0.129</td>
</tr>
<tr>
<td></td>
<td>0.77±0.14</td>
<td>0.78±0.16</td>
<td>0.03±0.18</td>
<td>0.803</td>
</tr>
<tr>
<td></td>
<td>0.80±0.09</td>
<td>0.85±0.16</td>
<td>0.04±0.15</td>
<td>0.129</td>
</tr>
</tbody>
</table>
| Values are presented as mean±standard deviation. GLA, γ-linolenic acid; ALA, α-lipoic acid; CI, confidence interval; BPI, brief pain inventory; DPN, diabetic peripheral neuropathy. * Analyzed by paired t-tests between baseline and week 12 in each group, † analyzed by independent t-tests assessing changes in values between the groups.

Safety

Regarding the laboratory parameters, there were no significant differences between the two groups in terms of body mass index or the levels of HbA1c, fasting glucose, total cholesterol, LDL-C, or triglycerides between baseline and after 12 weeks of treatment. However, high density lipoprotein cholesterol levels significantly decreased in the GLA group from 49.67±12.14 to 50.05±10.99 (P=0.04) (Table 5). Patients generally tolerated the treatment well, as no new safety concerns or events related to GLA were reported.

The numbers of patients experiencing TEADRs (total of 63 events in 44 subjects), which were defined as any event not
present prior to the initiation of treatment or any event already present that worsened in either intensity or frequency following exposure to the treatment, were 15 (31.2%) in the GLA group and 29 (55.8%) in the ALA group; the difference between the two groups was significant ($P=0.014$). Most of the events ($n=55, 87.3\%$) were considered to be transient and mild. The TEADRs that were reported in at least two subjects did not differ in frequency between the two groups (Supplementary Table 1). One GLA patient (0.02\%) and one ALA (0.02\%) patient discontinued the study treatment due to other causes (wrist fracture due to slipping and falling, and back pain due to a sprain, respectively); each adverse event was considered to have an “unlikely” causal relationship with the study medication as judged by the investigator. SAEs occurred in one GLA patient who experienced gastrointestinal bleeding and chondromalacia of the medial femoral condyle in both knees.

**DISCUSSION**

The present study demonstrated that T2DM patients with DPN who were treated with GLA over 12 weeks showed improvements in pain severity as measured by the VAS, and that GLA was noninferior to ALA. Additionally, the mean TSS score of the GLA group improved after 12 weeks of treatment, but none of the individual symptoms, except stabbing pain, exhibited a significant change compared to baseline. Although none of the TSS measures in the GLA group met the noninferiority criteria compared to ALA, the noninferiority of symptomatic improvements in DPN due to GLA compared to ALA was supported by the secondary outcomes for efficacy. The scores on the MNSI, mBPI-DPN, and EQ 5D after 12 weeks of treatment did not differ significantly between the GLA and ALA groups. However, there were no changes in the CPT measures (except at 2,000 Hz for GLA) or mean EQ 5D scores in either group. The overall treatment demonstrated a tolerable safety profile. A total of 55 mild adverse events were observed in 37 patients (22 events in 13 GLA subjects and 33 events in 24 ALA subjects), but all were transient and self-limited.

The pathogenesis and natural history of DPN remain largely unknown. However, hyperglycemia-triggered oxidative stress and defects in the microvasculature have complex interactions with neurovascular dysfunction, and both are associated with the progression of nerve damage, which makes it difficult or impossible to identify the favorable functional or structural effects of potential therapeutic modalities [30,31]. More specifically, the Neurological Assessment of Thioctic Acid in Diabetic Neuropathy (NATHAN) 1 trial showed that treatment with ALA (600 mg, once daily) slowed the progression of neuropathic deficits rather than improving these deficits, and that there were modest changes in measures of DPN in a placebo group after 4 years [30]. Another randomized trial observed improvements in neuropathic symptoms and neuropathic deficits, such as summed median and sural sensory nerve conduction velocities, in a placebo group after 1 year of observation, and reported that these changes were associated with improvements in metabolic variables, including glycemic control and serum triglyceride levels [32]. However, this study did not report differences in blood glucose or triglyceride levels be-

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**Table 5. Changes in BMI, HbA1c, glucose, and lipid profiles**

<table>
<thead>
<tr>
<th>Variable</th>
<th>GLA ($n=48$)</th>
<th>ALA ($n=52$)</th>
<th>P value&lt;sup&gt;a&lt;/sup&gt;</th>
<th>P value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI, kg/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>25.02±3.19</td>
<td>25.18±3.23</td>
<td>0.715</td>
<td></td>
</tr>
<tr>
<td>12 week</td>
<td>25.26±3.71</td>
<td>25.51±3.83</td>
<td>0.785</td>
<td>0.743</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>6.96±0.88</td>
<td>7.17±1.06</td>
<td>0.053</td>
<td>0.469</td>
</tr>
<tr>
<td>12 week</td>
<td>7.25±1.17</td>
<td>7.43±1.31</td>
<td>0.274</td>
<td>0.670</td>
</tr>
<tr>
<td>FPG, mg/dL</td>
<td>129.71±30.52</td>
<td>142.30±39.39</td>
<td>0.021</td>
<td></td>
</tr>
<tr>
<td>12 week</td>
<td>134.71±64.92</td>
<td>143.17±40.12</td>
<td>0.274</td>
<td>0.568</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>146.50±27.23</td>
<td>149.75±31.22</td>
<td>0.327</td>
<td></td>
</tr>
<tr>
<td>12 week</td>
<td>158.90±35.57</td>
<td>163.40±42.35</td>
<td>0.827</td>
<td>0.670</td>
</tr>
<tr>
<td>Triglyceride, mg/dL</td>
<td>137.02±75.97</td>
<td>130.10±67.79</td>
<td>0.243</td>
<td></td>
</tr>
<tr>
<td>12 week</td>
<td>153.21±104.71</td>
<td>150.67±80.20</td>
<td>0.941</td>
<td>0.878</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>49.67±12.14</td>
<td>50.05±10.99</td>
<td>0.040</td>
<td></td>
</tr>
<tr>
<td>12 week</td>
<td>51.83±14.24</td>
<td>51.10±14.28</td>
<td>0.353</td>
<td>0.572</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>69.52±27.84</td>
<td>74.05±28.40</td>
<td>0.217</td>
<td></td>
</tr>
<tr>
<td>12 week</td>
<td>77.34±30.17</td>
<td>80.66±35.10</td>
<td>0.703</td>
<td>0.407</td>
</tr>
</tbody>
</table>

Values are presented as mean±standard deviation.

BMI, body mass index; HbA1c, glycosylated hemoglobin; GLA, γ-linolenic acid; ALA, α-lipoic acid; FPG, fasting plasma glucose; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.

<sup>a</sup>Analized by paired $t$-tests between baseline and week 12 in each group, <sup>b</sup>analyzed by independent $t$-tests assessing changes in values between the groups.
neuropathic symptoms and deficits following treatment with ALA [21]. Other studies have reported that improvements in pain, scores on the Neuropathy Symptoms and Change (NSC) scale, and patients’ global assessments of efficacy were observed. For example, the Symptomatic Diabetic Neuropathy (ISLAND) study, in which patients with metabolic syndrome received oral treatment with 300 mg of ALA [32]. The patients exhibited significant improvements in endothelium-dependent flow-mediated vasodilatation of the brachial artery accompanied by reductions in plasma levels of interleukin-6 and plasminogen activator-1. Therefore, future studies should address whether pathogenetic-based therapies such as ALA or GLA will result in symptomatic relief that is mediated, at least in part, by improvements in the development and/or progression of DPN.

The present noninferiority study demonstrated that GLA was no worse for pain relief (as measured by the VAS and TSS) than ALA as an active comparator according to the noninferiority margin. A previous Korean study investigating the efficacy and safety of ALA in patients with DPN (n=61) found that treatment with oral ALA (600 mg/day) improved TSS scores at 4 weeks (4.4±1.7) and 8 weeks (3.1±1.7, P<0.01) compared to baseline (5.8±1.8), with tolerable safety [27]. Additionally, this study showed that individual symptoms such as pain, burning, paresthesia, and numbness improved after 8 weeks of treatment (all P<0.01). Similarly, another Korean study (n=38) showed that TSS scores significantly decreased at 4 weeks after treatment with ALA (600 mg, once daily) and further decreased after 8 weeks of treatment (all P<0.01). Based on the criterion of a change in TSS score ≥30% from baseline, the response rates in these studies were 77.3% and 71.4%, respectively. However, these open-label studies were neither randomized nor placebo-controlled. In the present noninferiority study, a PP analysis was conducted to protect against the risk of type I error that is associated with intention-to-treat analyses [39]. The present results showed that the CIs for the treatment effects were 0.500 (δ) for the VAS and 0.051 (δ) for the TSS as primary outcomes; the margins of noninferiority were pre-specified. Thus, based on VAS scores, GLA improved neuropathic symptoms in terms of relative efficacy compared to ALA for the treatment of DPN. There was no placebo arm due to the nature of the present study, thus it was possible to use the lower bound of the 95% CI to establish an efficacy advantage over placebo. As a result, it was confirmed that GLA had a clinically relevant superiority over placebo.

The cutoffs for the response rates of the outcome measures used for interventional studies of painful DPN have yet to be...
fully clarified. However, most studies have employed a response rate ranging from 30% to 50% [40]. In the present study, the response rate was defined as a ≥40% reduction in VAS score after 12 weeks of treatment. The GLA group had a 60.0% response, whereas the ALA group had a 42.1% response (P=0.127). A meta-analysis of intravenous ALA (600 mg/day for 3 weeks; n=1,258) for the treatment of DPN found that TSS scores exhibited a relative decrease of 24.1% from baseline, with 52.7% considered as responsive; i.e., ≥50% improvement in TSS score compared to 36.9% in the placebo group [18]. In that study, the relative difference between scores at baseline and at the end of the 12-week ALA treatment period was 31.7%. Therefore, the effects of ALA on neuropathic symptoms in patients with DPN observed in the present study appear to be comparable to those observed in previous studies. Further studies should be conducted to develop a uniform, validated, and internationally accepted range of outcome measures to compare the efficacies of treatments for painful DPN.

The present study had several critical limitations that should be considered. First, the lack of homogeneity among the subjects in terms of the clinical stage and degree of DPN and comorbidities, such as glycemic control, concomitant micro- or macrovascular complications, and emotional stress or depression, could be a major confounding factor. For example, estimations of the characteristics and/or severity of DPN-related pain vary within individuals during the course of DPN [41,42]. Second, the reasons for the discrepancies between the effects of GLA and ALA on the mBPI-DPN sub-scores were not fully understood. The differential effects of these antioxidative treatment modalities on the pathophysiology of nerve damage and how they result in different intensities of symptom profiles should be addressed in further studies. Third, the natural history and diabetes duration-dependent symptom phenotypes vary among patients with DPN [25]. The progressive degeneration and loss of peripheral nerve fibers in patients with T2DM results in abnormal excitability or insensitivity, which are associated with various troublesome issues in the lower extremities [25]. Therefore, the present 12-week treatment period with GLA or ALA may have been too short to allow for the achievement of clinically meaningful changes in neuropathic deficits that were observed previous studies [43,44]. Additionally, the favorable effects of 12 weeks of treatment with either GLA or ALA in the present study may not translate to the long-term management of patients with DPN. Finally, the present results regarding the efficacies of the medications for painful DPN were heterogeneous, and it will be difficult to directly compare these results with those of other studies. It is possible that the difficulties in defining and measuring neuropathic endpoints are associated with the heterogeneity of patients in terms of the diagnostic definition and clinical stages of DPN, metabolic control status, type of diabetes, the variety and non-identical attributes of symptom phenotypes, and the different treatment modalities for DPN [42]. Nonetheless, the present findings of improvements in neuropathic symptoms and the tolerability of the treatments in the absence of SAEs are encouraging, because GLA and ALA could be considered pathogenesis-based and symptomatic therapies. Additionally, the mechanism(s) of GLA and/or ALA underlying the improvements in neuropathic symptoms of GLA and/or ALA are not determined in this study, further studies through measurement of other serum markers for inflammatory or oxidative stress or using in vivo are needed.

In conclusion, the present trial demonstrated that the magnitude of efficacy of GLA treatment on pain severity (as measured by the VAS) over 12 weeks was comparable to that of ALA. Additionally, both treatments were well-tolerated and, therefore, GLA appears to be a reasonable treatment option for Korean patients with painful DPN. The present findings should be further validated by larger well-designed and high quality randomized controlled trials.

**SUPPLEMENTARY MATERIALS**

Supplementary materials related to this article can be found online at https://doi.org/10.4093/dmj.2019.0099.

**CONFLICTS OF INTEREST**

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**AUTHOR CONTRIBUTIONS**

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### Supplementary Table 1. Frequencies of TEADRs that occurred in at least two patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>GLA (n=48)</th>
<th>ALA (n=52)</th>
<th>P value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEADR</td>
<td>9 (18.75)</td>
<td>14 (26.92)</td>
<td>0.332&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Chronic bronchitis</td>
<td>2 (4.17)</td>
<td>1 (1.92)</td>
<td>-</td>
</tr>
<tr>
<td>Cold</td>
<td>0</td>
<td>4 (7.69)</td>
<td>-</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (2.08)</td>
<td>2 (3.85)</td>
<td>1.000</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (2.08)</td>
<td>2 (3.85)</td>
<td>-</td>
</tr>
<tr>
<td>Elevated blood pressure</td>
<td>0</td>
<td>2 (3.85)</td>
<td>-</td>
</tr>
<tr>
<td>Epigastric pain</td>
<td>2 (4.17)</td>
<td>1 (1.92)</td>
<td>1.000</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>1 (2.08)</td>
<td>2 (3.85)</td>
<td>0.333</td>
</tr>
<tr>
<td>Fractured wrist</td>
<td>2 (4.17)</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

Values are presented as number (%).

TEADR, treatment-emergent adverse drug reaction; GLA, γ-linolenic acid; ALA, α-lipoic acid.

<sup>a</sup>Treatment comparison of P values determined by Fisher's exact tests for categorical variables.

<sup>b</sup>Treatment comparison of P values determined by chi-square tests for categorical variables.
Supplementary Fig. 1. Study design. GLA, γ-linolenic acid; ALA, α-lipoic acid.
Supplementary Fig. 2. Patient distribution. GLA, γ-linolenic acid; ALA, α-lipoic acid. “Taken/administered prohibited medication(s),” Treatment compliance was defined as the intake of at least 80% of the trial medications.