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TREATMENT OF ALCOHOLIC POLYNEUROPATHY WITH VITAMIN B COMPLEX: A RANDOMISED CONTROLLED TRIAL

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Abstract — **Aims**: To evaluate the therapeutic efficacy and safety of BEFACT® Forte 'new formulation' and BEFACT® Forte 'old formulation' in the treatment of sensory symptoms of alcoholic polyneuropathy. **Methods:** A multi-centre, randomised, double-blind, placebo-controlled study was conducted on 325 patients with sensory symptoms and signs of alcoholic polyneuropathy. Patients were randomised to the 'old formulation' (i.e. vitamins B_1, B_2, B_6, and B_{12}), 'new formulation' [i.e. identical to the 'old formulation' with additional folic acid (vitamin B_9)], or placebo in a 1:1:1 ratio. One tablet of the study medication ('new formulation' or 'old formulation') or placebo was taken orally, three times a day, over a 12-week treatment period. **Results:** Therapeutic efficacy was assessed in 253 patients by measuring vibration perception threshold (biothesiometry), intensity of pain, sensory function, co-ordination, and reflex responses. Patients treated with the 'new formulation' or 'old formulation' showed significant improvement in the primary efficacy endpoint (vibration perception threshold at the big toe) and secondary efficacy endpoints in comparison to placebo. The active treatment groups were comparable to placebo in terms of safety. **Conclusions:** A specific vitamin B complex (with and without folic acid) significantly improved symptoms of alcoholic polyneuropathy over a 12-week treatment period.

INTRODUCTION

Chronic alcoholism is a global medical, social, and healthcare problem. Alcoholic polyneuropathy is a disorder of the peripheral nervous system that interferes with sensory, motor, and autonomic nerve function. In the Western hemisphere, alcoholic peripheral neuropathy is most prevalent in the 40- to 70-year-old age group and is encountered in both males and females (Ammedola *et al*., 2000; Zambelis *et al*., 2005). The clinical features of alcoholic polyneuropathy are similar to those of beri-beri [a deficiency of thiamine (vitamin B_1)] and primarily affects the muscular, cardiovascular, gastrointestinal, and nervous systems. Initial symptoms of alcoholic polyneuropathy are usually found in the lower extremities (Ammendola *et al*., 2001) and can affect both the sensory (numbness, paresthesia, loss of vibration, and position sense) and motor (weakness) systems. Symptoms can progressively extend into the proximal lower extremities and distal upper extremities, with patients showing degeneration of axons and reduction in the myelination of neural fibres. Severe alcoholic polyneuropathy may cause difficulty in walking, frequent falls, or paralysis.

In addition to the direct toxic effect of alcohol on autonomic and peripheral nerves, symptoms of alcoholic polyneuropathy are also a result of nutrient deficiencies (Pinelli, 1985; Zambelis *et al*., 2005). Malnutrition is common in alcoholics. Chronic alcoholics frequently have evidence of nutritional deficiency due to decreased dietary intake, reduced uptake, and impaired utilisation of nutrients (Mezey, 1980; Ryle and Thomson, 1984). Malnourished alcoholics tend to consume significantly more alcohol (Gloria *et al*., 1997), whilst also having increased nutritional requirements owing to the greater metabolic demands and the need for tissue repair (Ryle and Thomson, 1984). Alcohol-dependent individuals are therefore at higher risk of inadequate intake of several vitamins (Fairfield and Fletcher, 2002) and progression to alcoholic polyneuropathy. Furthermore, despite it being known that chronic alcoholics require relevant B-vitamin supplementation (Hell *et al*., 1976; Majumdar *et al*., 1981), no concise guidelines for the use of vitamin supplements by alcohol misusers currently exist in the United Kingdom.

The therapeutic use of vitamins meets two main objectives: preventing and treating either deficiencies or vitamin-dependent metabolic diseases (Naurath *et al*., 2001). Water-soluble vitamins B_1 (thiamine), B_2 (riboflavin), B_6 (pyridoxine), B_9 (folic acid), and B_{12} (cyanocobalamin) are co-factors in numerous enzymatic activities and proton and electron transfers (Krautler, 2005), and experimental studies have demonstrated that chronic ethanol consumption may contribute to the alterations of vitamin B status (Kim and Roe, 1985; Laforenza *et al*., 1990).

Two specific formulations of B-vitamins for the treatment of alcoholic polyneuropathy have been developed. BEFACT® Forte 'old formulation' contains vitamin B_1, B_2, B_6, and B_{12} and is already on the market in Belgium. BEFACT® Forte 'new formulation' contains vitamin B_1, B_2, B_6, B_{12}, and, in addition, vitamin B_9 (folic acid). The addition of vitamin B_9 (folic acid) was intended to increase the efficacy of the treatment in alcoholic polyneuropathy as folate deficiency has been shown to contribute to the development of alcoholic polyneuropathy (Gimsing *et al*., 1989).

The present clinical study was designed to evaluate the therapeutic efficacy and safety of BEFACT® Forte 'new formulation' and BEFACT® Forte 'old formulation' in the treatment of sensory symptoms of alcoholic polyneuropathy.

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PATIENTS AND METHODS

Patients

Patients were eligible to participate in the study if they showed sensory symptoms and signs of alcoholic polyneuropathy (as diagnosed by a nerve conductance study), were alcoholic and fulfilled at least three of the criteria of the International Classification of Diseases (ICD-10, World Health Organisation, 1993) and had a vibration perception threshold (biothesiometry) at the big toe of <3, according to the method of Rydel and Seiffer (1903).

Patients were not entered into the study if they: had a history of alcoholic polyneuropathy for >2 years, consumed >50 U of alcohol/day (approximately two bottles of spirits), had diabetes mellitus, Parkinson's disease, Wernicke–Korsakoff syndrome, epilepsy (treated with phenytoin, phenobarbital, primidone, or carbamazepine), non-alcoholic neuropathy, any significant cardiac disease, had skin eruptions (rashes) in the regions of assessment, women who were pregnant or lactating, were known carriers of HIV or syphilis, had allergies to any constituents of the investigational medication, were drug dependent, or abused illicit drugs (including barbiturates and benzodiazepines), had taken any prohibited medication (e.g. disulfiram), had taken vitamin supplements within the previous three months, or if they had participated in any other clinical trial within 3 months of the screening visit.

Study design

The experimental design was a multi-centre, randomised, double-blind, placebo-controlled study. The study was conducted in accordance with the Declaration of Helsinki (Scotland, October 2000), International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and with local laws and regulations relevant to the country of conduct. The independent ethics committees approved the protocol for all participating centres (i.e. four centres in Poland and seven in Ukraine). All patients enrolled in the study provided written informed consent (in a sober state) before randomisation, and were enrolled between March 2004 (first patient, first visit) and July 2005 (last patient, last visit). The study was strictly monitored according to the ICH GCP guidelines, by a Polish Contract Research Organisation.

There was a screening period (Visit 1) at 7–14 days prior to randomisation. At Visit 2 (Week 0), each patient was randomised (1:1:1 ratio using a validated automated system) to receive either BEFACT® Forte 'new formulation', BEFACT® Forte 'old formulation' or placebo followed by a 12-week treatment period, with clinical assessments at Week 0 (Visit 2), Week 6 (Visit 3) and Week 12 (Visit 4).

Study medication was manufactured as a sugar-coated tablet: BEFACT® Forte 'old formulation': each tablet contained vitamin B_1 (250 mg), vitamin B_2 (10 mg), vitamin B_6 (250 mg), and vitamin B_{12} (0.02 mg); BEFACT® Forte 'new formulation': each tablet contained vitamin B_1 (250 mg), vitamin B_2 (10 mg), vitamin B_6 (250 mg), vitamin B_{12} (0.02 mg), and folic acid (1 mg). Placebo tablets were visually identical to the BEFACT® Forte tablets but lacked the active components.

Patients took one tablet orally, three times per day (morning, noon, and night) with 240 ml of water during a meal. All the tablets were supplied in blister alu/PVC (10 tablets/blister) packed in boxes, with each box containing the medications for a period of 6 weeks with extra dose for 8 days (150 tablets). Study medication was dispensed at Visit 2 (Week 0) and Visit 3 (Week 6) and was self-administered by the patients, who were provided with instructions on dosing.

To maintain the double-blind conditions, the investigators and site personnel, as well as personnel involved in field monitoring, data handling, or the conduct of the trial were blinded to the study medication. Except in case of emergency, trial drug codes were not available to the above personnel until the completion of the trial and final data review.

Efficacy assessments

Vibration perception threshold was measured for the big toe, inside ankle, first metatarsal bone and mid-tibia for both the left and the right leg at every visit (Visits 1, 2, 3, and 4). Measurement was taken using a 128 Hz graduated tuning fork according to the method of Rydel and Seiffer (1903). A vibration perception threshold of 8 was defined as normal and 0 corresponded to complete impairment of vibration perception. The mean was determined from three individual measurements at each point. Each patient completed the short-form of McGill's pain questionnaire (Melzack, 1987) at every visit (Visits 1, 2, 3, and 4), which included subjective assessments of total pain, visual analogue scale (VAS) measurement, and present pain intensity (PPI) score.

The two-point discrimination sensory test took place at every visit (Visits 1, 2, 3, and 4), whereby the spatial discriminative ability of the skin was determined by measuring minimum separable distance between two tactile point stimuli. The patient was asked to expose the area of skin being tested and close their eyes. The investigator used a two-pointed calliper and gently touched the person using the two points. Starting with the points 20 mm apart, the distance apart was decreased until the patient could no longer feel two distinct points. The investigator then recorded the number of millimetres at which the patient could only just feel one point. This test was performed on the big toe and mid-tibia of each leg.

The eye–nose coordination test took place at every visit (Visits 1, 2, 3, and 4). It was assessed with the patient standing with their legs together, arms horizontal, and eyes open on one occasion and eyes shut on the second. The patient was asked to touch the tip of their nose with each index finger alternatively. They were asked to repeat this three times. The investigator then scored them as 'impaired' or 'no impairment'—'impaired' being unable to touch the tip of their nose in one move or missing the nose.

The knee-jerk and Achilles reflex were measured at every visit (Visits 1, 2, 3, and 4). For the knee-jerk reflex the patient sat on a chair with their legs crossed or dangling. The investigator then tapped one patellar tendon just below the kneecap with a reflex hammer. The investigator repeated this for the other patellar tendon. For the Achilles reflex the investigator lightly tapped the Achilles tendon with a reflex hammer and repeated for each leg. The investigator scored each reflex as 'increased', 'normal', 'decreased', or 'absent'.

Safety assessments

All patients were given a diary card to record adverse events (AEs) and any medications that were taken concomitantly. A new diary was given to the patient on Visits 1, 2, and 3 and returned on Visits 2, 3, and 4. Each AE was rated for severity and potential implication to the study treatment.

Blood samples were taken at Visit 1 (screening) and at Visit 4 (Week 12) and standard haematological and biochemical analyses performed. Vital signs (systolic and diastolic blood pressure, pulse rate, and oral temperature) were measured at every visit (Visits 1, 2, 3, and 4).

Statistical analysis

Sample size calculations considered the three major parameters—vibration perception threshold, pain intensity and overall neuropathy symptom score. For vibration perception, taking the likely difference between active and placebo to be 0.6 U with a standard deviation (SD) of 0.5, a significance level of 0.05 and power of 80%, then the sample size was calculated as 20 patients per group. For pain intensity, basing calculations on Woelk *et al*. (1998), the sample size was 66 patients per group. For overall neuropathy symptom score, the sample size was calculated to be 36 patients per group. Therefore, to encompass all parameters, it was planned to randomise 66 patients to each of the three treatment groups. To achieve this it was anticipated that 250 patients would be enrolled, including a drop-out of 25%.

During the study, all patients randomised at Centre 5 (Lublin, Poland, $n = 72$) were discontinued because an audit revealed indications that some data at this site might have been unreliable, that required source data was not available for cross-validation, and that GCP might not have been followed. These patients were included in the safety analysis but not the efficacy analysis. To ensure the required sample size was met, 72 extra patients were recruited from the other sites

The study population analysed for efficacy was an intention-to-treat (ITT) population, defined as all randomised patients, excluding patients at Centre 5. A supportive efficacy analysis was conducted on the per protocol (PP) population, defined as all randomised patients who completed the study as per protocol. Safety data were analysed using the Safety population, defined as all randomised patients.

The primary comparisons were between BEFACT® Forte 'new formulation' versus placebo and BEFACT® Forte 'old formulation' versus placebo. To control the rate of false positive conclusions (type I error rate α) a closed-testing procedure (i.e. hierarchical order for testing null hypotheses) was used in a strict prefixed order whereby first BEFACT® Forte 'new formulation' was tested against placebo. Only if there was no significant difference between BEFACT® Forte 'new formulation' and placebo at the significance level α was the scheme to proceed to test BEFACT® Forte 'old formulation' against placebo, also at level α. Therefore, no adjustments due to multiple comparisons were necessary.

The primary efficacy endpoint was the change from baseline (Week 0) to Visit 4 (Week 12) in the vibration perception threshold at the big toe in patients with alcoholic polyneuropathy. The secondary efficacy endpoints were the change from baseline (Week 0) to Visit 4 (Week 12) in: (i) the vibration perception thresholds (biothesiometry) at the inside ankle, metatarsal bone, and mid-tibia, (ii) the intensity of pain (i.e. total pain, VAS measurement, and PPI score), assessed by the short form of McGill's pain questionnaire, (iii) sensory function, assessed using the two-point discrimination test at the great toe and tibia, (iv) co-ordination assessed using the eye–nose test, and (v) reflex response assessed using the knee-jerk reflex and Achilles reflex. The comparison of treatment groups was performed using Wilcoxon rank sum test for the changes from baseline (Week 0) to Visit 3 (Week 6) and Visit 4 (Week 12) at the two-sided 5% level of significance. Comparisons of new formulation versus placebo and old formulation versus placebo with 95% confidence intervals (CI) were performed. The overall comparability of treatment groups at each visit was performed using the Kruskal–Wallis test [with the exception of eye–nose coordination (Fisher's Exact test) and reflex responses (descriptive statistics only)]. Safety endpoints were summarised using descriptive statistics.

RESULTS

Patient characteristics

A total of 394 patients were screened and a total of 325 patients were randomised (see Fig. 1). For each treatment group, 109 patients received the new formulation, 107 patients received the old formulation, and 109 patients received placebo. However, 24 patients from each group (i.e. 72 patients) at Centre 5 were discontinued and were included in the Safety population only. Therefore, a total of 253 patients were included in the ITT population. Overall, 204 patients completed the study after 49 patients were withdrawn [predominantly as patients were lost to follow-up (Fig. 1)]. A small number of patients in each group were excluded from the PP population.

Baseline characteristics of patients in the ITT population are shown in Table 1. There were no statistically significant differences between groups for age ($P = 0.104$, Kruskal–Wallis test), gender ($P = 0.811$, Fisher's Exact test), duration of alcoholic polyneuropathy ($P = 0.858$, Kruskal–Wallis test), or prior alcohol usage at Visit 1 (screening, $P = 0.946$) and Visit 2 (Week 0, $P = 0.608$). During the study, alcohol usage prior to Visit 3 (Week 6, $P = 0.828$) or prior to Visit 4 (Week 12, $P = 0.450$, Kruskal–Wallis test) was not significantly different between treatment groups.

Efficacy evaluation

Primary and secondary efficacy endpoints are shown in Tables 2 and 3. For the ITT population, the primary efficacy endpoint, vibration perception threshold at the big toe (left and right legs), showed a statistically significant difference between treatment groups at Visit 3 (Week 6) ($P < 0.001$) and Visit 4 (Week 12) ($P < 0.001$). The greatest mean increase from baseline (Week 0) to Visit 4 (Week 12) for the left leg was +1.48 (new formulation) and +1.67 (new formulation) for the right leg. The change from baseline (Week 0) to Visit 4 (Week 12) was significantly different between the new formulation and placebo ($P < 0.001$) and between the old formulation and placebo ($P < 0.001$). Furthermore, the change from baseline (Week 0) to Visit 3 (Week 6) was

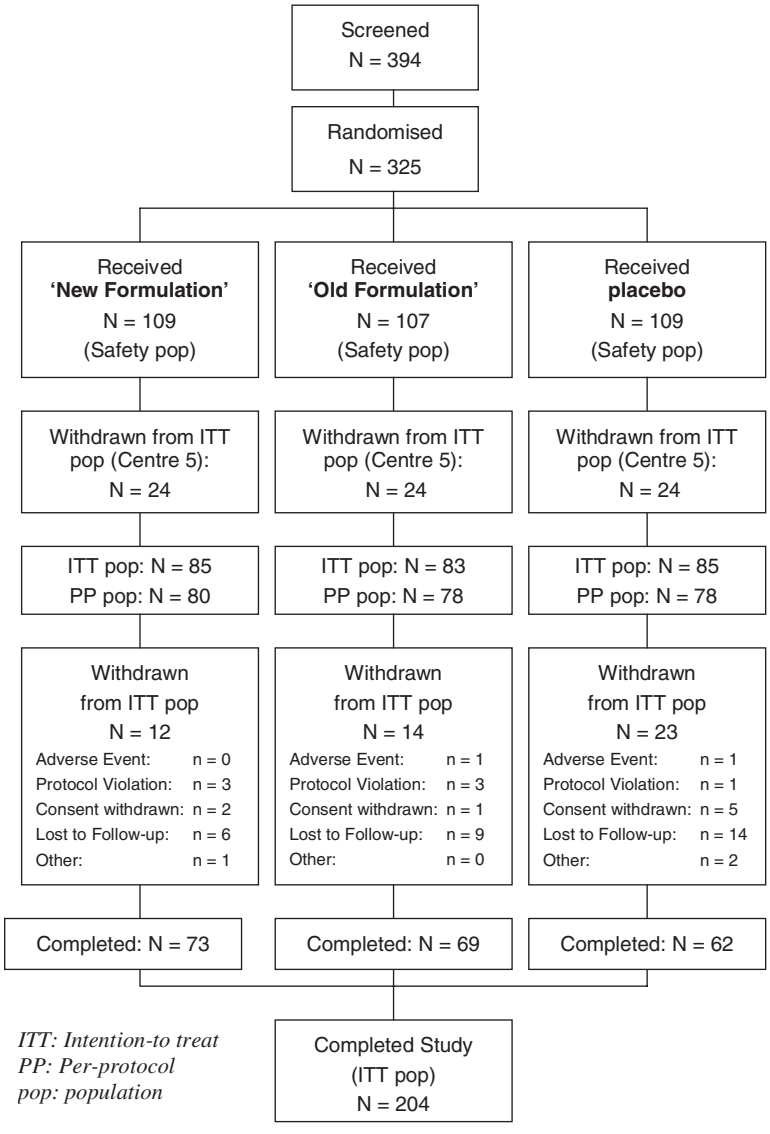

Fig 1. Recruitment of patients to the ITT sample and their retention.

Table 1. Patients' characteristics

	New formulation (N = 85)	Old formulation (N = 83)	Placebo (N = 85)
Caucasian	85	83	85
Age (years)	47 (9.1)	50 (9.9)	50 (9.6)
Gender (male/female)	65/20	64/19	62/23
Duration of Alc. PN (years)	0.6 (0.6)	0.6 (0.6)	0.6 (0.6)
Alcohol consumed (U)			
Prior to Visit 1, Screening	4.0 (7.53)	5.3 (9.88)	4.2 (7.99)
Prior to Visit 2, Week 0	4.6 (8.36)	4.7 (7.34)	4.7 (7.97)
Prior to Visit 3, Week 6	4.7 (7.92)	3.8 (7.62)	4.7 (8.02)
Prior to Visit 4, Week 12	3.2 (5.90)	4.3 (8.08)	5.8 (10.09)

Data are presented as mean (SD) for the ITT population.
1 U corresponds to 10 g ethanol.
Alc. PN = alcoholic polyneuropathy.

also significantly different between the new formulation and placebo ($P < 0.001$) and between the old formulation and placebo ($P < 0.001$).

For the secondary efficacy endpoints, vibration perception threshold at the inside ankle, metatarsal bone, and mid-tibia bone all showed statistically significant differences between treatment groups at Visit 4 (Week 12). The changes from baseline (Week 0) to Visit 3 (Week 6) and baseline to Visit 4 (Week 12) were significantly greater in the new formulation versus placebo ($P < 0.001$) and for the old formulation versus placebo ($P < 0.001$) for both left and right legs. The vibration perception threshold results for the PP population were similar to the ITT population results.

For the ITT population, the greater reduction in total pain from baseline (Week 0) occurred at Visit 4 (Table 2). For both the ITT and PP populations, the change from baseline (Week 0) to Visit 4 (Week 12) was significantly greater for the new formulation versus placebo ($P < 0.001$) and for the old formulation versus placebo ($P < 0.001$). Similar statistically significant results also occurred at Visit 3 (Week 6). For the ITT and PP populations, the new and old formulation groups showed statistically significantly greater reductions in mean VAS measurements and PPI scores at Visit 3

Table 2. Efficacy parameters: change from baseline

	New formulation ($N = 85$)	Old formulation ($N = 83$)	Placebo ($N = 85$)
Vibration perception threshold			
Left big toe*,†	+1.48 (1.006)	+1.38 (0.784)	+0.52 (0.766)
Right big toe*,†	+1.67 (1.052)	+1.44 (0.856)	+0.59 (0.724)
Left inside ankle*,†	+1.22 (0.897)	+1.24 (0.906)	+0.31 (0.886)
Right inside ankle*,†	+1.23 (0.958)	+1.25 (0.893)	+0.43 (0.883)
Left metatarsal bone*,†	+1.19 (1.015)	+0.97 (0.748)	+0.35 (0.933)
Right metatarsal bone*,†	+1.12 (0.940)	+1.06 (0.981)	+0.40 (0.887)
Left mid-tibia bone*,†	+1.15 (1.135)	+1.08 (0.899)	+0.28 (0.890)
Right mid-tibia bone*,†	+1.11 (1.062)	+1.07 (0.803)	+0.29 (0.955)
McGill's pain questionnaire			
Total pain score*,†	–8.6 (7.55)	–7.5 (6.76)	–3.8 (8.18)
VAS measurement*,†	–35.0 (18.61)	–34.9 (20.32)	–9.5 (18.65)
PPI score*,†	–1.7 (1.07)	–1.8 (1.12)	–0.5 (1.00)
Sensory function			
Left big toe*,†	–4.23 (5.963)	–4.36 (7.653)	–0.82 (2.957)
Right big toe*,†	–3.77 (5.943)	–4.71 (8.990)	–0.73 (3.626)
Left mid-tibia*,†	–10.53 (17.85)	–10.90 (15.77)	–1.70 (8.08)
Right mid-tibia*,†	–11.06 (16.96)	–10.56 (13.22)	–2.38 (8.32)

Data are presented as mean change from baseline (Week 0) to Visit 4 (Week 12) (SD) for the ITT population.
*$P < 0.001$: new formulation versus placebo (Wilcoxon-Rank Sum Test).
†$P < 0.001$: old formulation versus placebo (Wilcoxon-Rank Sum Test).

Table 3. Efficacy parameters

	New formulation ($N = 85$)	Old formulation ($N = 83$)	Placebo ($N = 85$)
Improved eye–nose coordination (%)			
Eyes open	11 (12.9)	13 (15.7)	12 (14.1)
Eyes closed*,†	18 (21.2)	17 (20.5)	6 (7.1)
Normal reflex responses (Week 0/Week 12)			
Left knee-jerk reflex	13/38	14/32	19/15
Right knee-jerk reflex	13/37	14/32	20/14
Left Achilles reflex	2/20	2/19	3/3
Right Achilles reflex	2/20	3/18	3/3

Data presented are number of patients who showed improvement in eye–nose coordination at Visit 4 (Week 12) and the number of patients who had a normal reflex response at Visit 2 (Week 0) and Visit 4 (Week 12) for the ITT population. Percentages are based on the number of patients in the respective treatment group.
*$P < 0.001$: new formulation versus placebo (Fisher's Exact Test).
†$P < 0.001$: old formulation versus placebo (Fisher's Exact Test).

(Week 6) and Visit 4 (Week 12) compared with placebo ($P < 0.001$).

The change in sensory function (i.e. two-point discrimination test at the big toe and mid-tibia) from baseline (Week 0) to Visit 4 (Week 12) was significantly different between the new formulation and placebo ($P < 0.001$) and between the old formulation and placebo ($P < 0.001$). Also, the change from baseline (Week 0) to Visit 3 (Week 6) was significantly different between the new formulation and placebo ($P < 0.05$) and between the old formulation and placebo ($P < 0.05$).

For the ITT population, the improvement in eye–nose coordination (eyes closed) from baseline (Week 0) to Visit 4 (Week 12) showed a significant difference between treatment groups (Table 3). The number of patients showing an improvement between baseline (Week 0) and Visit 4 (Week 12) was significantly greater in the new formulation and placebo ($P = 0.026$) and between the old formulation and placebo ($P = 0.037$). Similar results were shown for the PP population.

Reflex responses (knee-jerk reflex and Achilles reflex) showed some improvement in the BEFACT® Forte treatment groups when compared with the placebo group, in that there was an increase in the number of patients with a normal reflex response at Visit 4 (Week 12).

Table 4. Summary of adverse events

	New formulation ($N = 85$)	Old formulation ($N = 83$)	Placebo ($N = 85$)
Number of patients with an AE	46	39	42
Number of AEs	165	154	187
Most frequent AEs (⩾5%)			
Headache (%)	51 (30.9)	57 (37.0)	67 (35.8)
Asthenia (%)	7 (4.2)	10 (6.5)	14 (7.5)
Nausea (%)	7 (4.2)	6 (3.9)	10 (5.3)
Back pain (%)	6 (3.6)	4 (2.6)	11 (5.9)
Dyspepsia (%)*	0	11 (7.1)	2 (1.1)

Data presented are for the Safety population.
Percentages are based on the number of AEs in the respective treatment group.
*$P < 0.05$: Chi-squared test.

Safety evaluation

There were 506 AEs in 127 patients [39.1% (Safety population)]. A similar number of patients experienced an AE in each treatment group (Table 4). The majority of all AEs were either mild (359 AEs) or moderate (146 AEs) with one severe AE [headache (placebo group)].

The most frequent AE was headache, which did not show a statistically significant difference between treatment groups ($P = 0.326$, Chi-squared test). The only AE that showed a significant difference in frequency between groups was dyspepsia ($P = 0.013$, Chi-squared test). However, the 11 AEs in the old formulation group occurred in two patients and were considered unrelated to the study drug, whilst the two AEs in the placebo group occurred in two patients and were considered related.

Safety haematology and biochemistry evaluations generally showed little change from screening to Visit 4 (Week 12) for each treatment group, and any difference between treatment groups was not considered to be clinically significant (Table 5). Vital signs showed little change from baseline (Week 0) to Visit 4 (Week 12) for all treatment groups.

DISCUSSION

In this multi-centre, randomised, double-blind, placebo-controlled, parallel study in patients, the efficacy of treating alcoholic polyneuropathy with BEFACT® Forte 'new formulation' and BEFACT® Forte 'old formulation' during 12 weeks' was confirmed in comparison to placebo.

There are few examples in the literature of specific vitamin B complexes being used in the treatment of alcoholic polyneuropathy. However, several studies investigating the effects of benfotiamine (a lipid-soluble derivative of vitamin B_1 with high bioavailability) on polyneuropathy

Table 5. Summary of laboratory evaluations

	New formulation (N = 109)	Old formulation (N = 107)	Placebo (N = 109)
ESR (mm/h)	–4.1 (9.8)	–3.4 (13.2)	–5.7 (16.8)
Leukocytes ($\times 10^9$/l)	+0.02 (1.94)	+0.07 (2.14)	+0.40 (1.61)
ALT (IU/l)	–0.6 (35.8)	+2.6 (25.7)	+1.3 (73.5)
AST (IU/l)	+2.4 (33.2)	+2.4 (36.7)	+9.0 (131.3)
GGT (IU/l)	–1.5 (44.9)	+17.0 (117.3)	–6.3 (61.9)
Glucose (mmol/l)	+0.02 (0.95)	+0.17 (1.14)	+0.27 (1.14)
Total Cholesterol (mmol/l)	+1.3 (4.9)	–0.3 (5.5)	–0.7 (4.5)

Blood samples were taken at screening and at Visit 4 (Week 12). Data presented are mean (SD) change from Visit 1 (screening) to Visit 4 (Week 12) for the Safety population.
ESR: erythrocyte sedimentation rate; ALT: alanine aminotransferase; AST: aspartate aminotranferase; GGT: gamma-glutamyl transferase.

have shown significant improvements in vibration perception threshold (Woelk *et al*., 1998), nerve conduction velocity (Stracke *et al*., 1996), neuropathy score and pain (Anisimova and Danilov, 2001; Haupt *et al*., 2005). These studies highlight the improvements in sensory and motor function in patients with polyneuropathy when treated with mono- or poly-vitamin formulations. The results from the present study have also shown improvements in the symptoms of alcoholic polyneuropathy using a specific vitamin B complex.

In the present study, the greatest mean improvement in vibration perception threshold at the big toe was observed at Visit 4 (Week 12) in the new and old formulation groups in comparison to placebo, with significantly greater values also recorded at Visit 3 (Week 6). These improvements were shown in both the left and right leg, which adds support to the effectiveness of the active treatments. Vibration perception threshold at the inside ankle, metatarsal bone, and mid-tibia bone was significantly greater in the new and old formulation groups at Visit 4 (Week 12) in comparison to placebo. The increase in vibration perception threshold indicates an improvement in the conductivity of the large myelinated fibres, which detect vibration and convey afferent information to the central nervous system. Improvement in sensory function was also established using the two-point discrimination test, which was statistically significantly greater for the new and old formulation groups at Visit 3 (Week 6) and Visit 4 (Week 12) in comparison to placebo.

The assessment of pain intensity using the short-form of McGill's pain questionnaire showed a significantly greater reduction in total pain score at Visit 3 (Week 6) and at Visit 4 (Week 12) for the new and old formulation in comparison to placebo. Similar results were shown when patients were assessed using the VAS and PPI, thus providing a clear indication that pain intensity was reduced at Week 6 and at Week 12 in patients treated with BEFACT® Forte new or old formulation. These results are particularly important as reduction in pain intensity is clinically relevant. Similar findings were reported by Haupt *et al*. (2005) and Simeonov *et al*. (1997) who used combinations of benfotiamine and cyanocobalamine (vitamin B_{12}) to significantly improve pain in the treatment of painful peripheral polyneuropathy.

The present study showed a significant improvement in eye–nose coordination and an improved reflex response over 12 weeks in patients treated with BEFACT® Forte in comparison with placebo. Woelk *et al*. (1998) also showed a tendency for improved coordination in patients with alcoholic polyneuropathy who were treated with benfotiamine, vitamin B_6 and B_{12}. These results provide further evidence of the positive effect on associative cerebellar and motor function when treated with BEFACT® Forte.

In terms of Safety population, a similar percentage of patients experienced an AE in each treatment group, with the most common AEs being headache and asthenia. Although dyspepsia occurred more frequently in the old formulation group (11 AEs in two patients), no incidents of dyspepsia were considered related to the study drug. Two AEs of dyspepsia occurred in the placebo group that were considered related, thus suggesting that these gastrointestinal events were symptoms of the disease and not related to the investigational drugs. The absence of any treatment-related change in clinical laboratory evaluations or vital signs also adds support to the safety of BEFACT® Forte new and old formulations.

Toxicity studies in animals have shown no evidence of teratogenic, mutagenic, or carcinogenic effect of vitamins B_1, B_2, B_6, and B_{12}, whilst toxicity in man is very low and adverse reactions are highly unusual. Woelk *et al*. (1998) reported no treatment-related AEs in their study population of alcoholic polyneuropathy patients who received either benfotiamine, benfotiamine in combination with vitamin B_6 and B_{12}, or placebo.

The direct toxic effect of alcohol on peripheral nerve fibres is thought to be the main etiologic factor of alcoholic polyneuropathy (Monforte *et al*., 1995; Kucera *et al*., 2002; Zambelis *et al*., 2005) with impaired vitamin B utilisation also involved (Kucera *et al*., 2002; Zambelis *et al*., 2005). Experimental studies have demonstrated that chronic ethanol consumption may contribute to the disturbance of vitamin B status in the body and may explain why alcoholics tend to be deficient in this group of vitamins. The present study has shown that treatment with a specific vitamin B complex significantly improves the symptoms of alcoholic polyneuropathy and therefore suggests that impaired neural (sensory and motor) function may be reversed.

There are a growing number of reports linking folic acid deficiency in alcoholic patients to peripheral polyneuropathy (Gimsing *et al*., 1989; Lopez-Hernandez *et al*., 2003). The addition of folic acid to the new formulation was intended to increase the efficacy of the treatment in alcoholic polyneuropathy. Although this study was not powered to distinguish between the new and the old formulation, both formulations showed similar significant improvements in terms of the primary and secondary efficacy endpoints in comparison with the placebo.

CONCLUSIONS

A specific vitamin B complex (with and without folic acid) is clinically efficacious in the treatment of patients with alcoholic polyneuropathy over a 12-week treatment period in comparison to placebo. The two formulations tested similar to placebo in terms of safety.

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