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A Comparative Placebo-Controlled Clinical Trial of the Efficacy and Safety of Glatiramer Acetate 20 mg in Patients with Remitting Multiple Sclerosis: First-Year Study Results

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Objective. To seek evidence that Timexon (BCD-063, glatiramer acetate, Biocad, Russia) and Copaxone-Teva (Teva Pharmaceuticals Ltd., Israel) have similar efficacies in patients with remitting multiple sclerosis. **Materials and methods.** A multicenter, double-blind, placebo-controlled, comparative, randomized, phase III study included 158 patients with confirmed diagnoses of remitting multiple sclerosis. Patients were randomized to the BCD-063, Copaxone-Teva, and placebo groups at a ratio of 2:2:1. **Results and conclusions.** Efficacy analysis at 48 weeks of treatment demonstrated that there were no differences between the BCD-063 and Copaxone-Teva groups in terms of MRI parameters or exacerbation frequency. Assessment of the primary endpoint (number of MRI-confirmed exacerbations per patient per year) showed that the mean number of exacerbations was 0.098361 (0.351422) in the BCD-063 group, 0.098361 (0.351422) in the Copaxone-Teva group, and 0.178571 (0.390021) in the placebo group. Assessments on the EDSS and MSFC also demonstrated that there were no differences between the BCD-063 and Copaxone-Teva groups. Both BCD-063 and Copaxone-Teva had favorable safety profiles. These data provide evidence of the therapeutic equivalence of BCD-063 (Biocad, Russia) and Copaxone-Teva, which is an important aspect for further introduction of the reproduced glatiramer acetate formulation into the treatment of multiple sclerosis.

Keywords: remitting multiple sclerosis, glatiramer acetate, BCD-063.

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) and one of the commonest neurological causes of the inability to work among young patients. Increases in the morbidity of MS in recent years have been by 5.5% per year, indicating that every year more than 5000 young people become untreated patients [1, 4]. At the beginning of illness, MS patients often lose the ability to work, while restrictions to self-care devel-

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op at the later stages; these and the early signs of disease make MS a disease of major social importance. By 10 years after onset, up to 50% of patients have restrictions in work activities, while by 15 years more than 50% have level II disability, increasing to level I when MS has been present for more than 20 years [2].

The high efficacy of glatiramer acetate (GA) for the treatment of MS patients is now regarded as demonstrated. GA (proprietary name Copaxone-Teva) was approved by the FDA as an agent for the out-patient treatment of patients with the active form of remitting MS in 1996 [3, 4]. GA was subsequently approved for use in many other countries.

The Russian glatiramer acetate formulation Timexon (BCD-063) from Biocad, Russian (Registration certificate No. LP-003875) has identical composition and dosage as the original formulation Copaxone-Teva. The equivalence of its physicochemical and biological properties with those of the original formulation has been demonstrated in comparative in vitro and in vivo preclinical studies.

With the aim of demonstrating the similar efficacies of Timexon (BCD-063, Biocad, Russia) and Copaxone-Teva (Teva Pharmaceutical Industries, Israel), an international multicenter, double-blind, placebo-controlled, comparative, randomized, phase III clinical trial was performed with active reference agent and placebo in patients with RMS (clinical trial registration No. RKI No. 346 of June 10, 2013).

Materials and Methods. The study was based on the hypothesis that Timexon (henceforth BCD-063, glatiramer acetate, Biocad, Russia) is no less effective than Copaxone-Teva (the "non-inferiority" hypothesis).

The study included patients aged 18–55 years of both genders with confirmed diagnoses of MS in terms of the MacDonald criteria (2005) with the remitting course. The duration of RMS was more than one year at screening; during the 12 months before randomization (visit 0), patients had had at least one exacerbation or at least one identified focus accumulating gadolinium on T1 MRI scans. Total EDSS scores were 0–5.5. Patients were neurologically stable (without exacerbations) during the four weeks prior to randomization (visit 1). Patients of both genders and their sexual partners with preserved reproductive functions used reliable contraception starting on the screening day and continuing for four weeks after the last drug dose.

The study excluded patients with secondary progressive and primary progressive forms of MS and other diseases which might affect assessment of the severity of the symptoms of the main disease (masking, exacerbating, or altering the symptoms of the main disease or inducing clinical signs and changes in laboratory and instrumented investigations similar to those of MS).

The study used the original GA formulation, its reproduced analog, and a placebo. The dose of study drug used in the present study, the means of use, and the dosage regime were selected in accordance with the instructions for medical use of Copaxone-Teva (registration certificate No. LS-000384): daily, s.c., at a dose of 20 mg (one full syringe for injection) once daily, preferably at the same time of day during the first 48 weeks of the study.

Patients were randomized to the BCD-063, Copaxone-Teva, or placebo groups at a ratio of 2:2:1. During the 48 weeks of the study, the patients in these groups used the corresponding formulations (BCD-063, Copaxone-Teva, or placebo) by the same regime.

Confirmed exacerbations of MS during the study were treated with i.v. methylprednisolone infusions at a dose of 1000 mg/day for five days.

The first stage in the study continued for 48 weeks (12 months), during which the efficacy and safety of the treatments used were studied. Endpoints linked with exacerbations and endpoints in terms of MRI scan parameters were assessed.

The analysis included assessment of efficacy using the blind period of the study, when comparisons between the three groups (BCD-063, Copaxone-Teva, and placebo) were performed after use to 48 weeks.

Objective measures of efficacy were obtained by ensuring that the specialists reporting MRI scan data were not familiar with which drug the patients received.

Inclusion of patients randomized in the study in the efficacy and safety analysis but lost to the study before the first drug dose (intention to treat, ITT) contributed no efficacy or safety information relating to the study treatments. The optimum population for studying efficacy and safety measures in the present study was a modified ITT population (mITT), which included data from all patients receiving at least one dose of study drug, reference agent, or placebo without leading to artificial reductions in the numbers of adverse events or exacerbations which might occur in patients terminating treatment early in the study (as in selecting a "per protocol" population). Selection of the mITT population provided for the fullest possible assessment of the efficacy and safety of the trial therapy.

Final analysis of efficacy included 150 patients (61 in the BCD-063 group, 61 in the Copaxone-Teva group, and 28 patients in the placebo group). Of the 158 patients, three patients were not included in the main efficacy analysis as they did not receive any doses of the test or reference formulations or placebo. Of the 155 patients who received treatment in the framework of the study, five patients were excluded from the efficacy analysis (two from the Copaxone-Teva group and three from the placebo group) due to contravention of the inclusion/exclusion criteria.

The efficacy analysis based on the dynamics of MRI measures included 121 patients from the population of mITT-150 patients (of which 136 patients completed the study) who entered the efficacy analysis in terms of exacerbation frequency. Some patients were lost to the study before repeat MRI such that analysis of changes in MRI measures was impossible. All three groups were comparable in terms of age and height/weight characteristics.

TABLE 1. Characteristics of Groups of Patients Included in the Efficacy Analysis (n = 150)

Parameter	Group 1: BCD-063 (n = 61)		Group 2: Copaxone-Teva (n = 61)		Group 3: placebo (n = 28)		p
Duration of illness (from onset of first symptoms to recruitment to the clinical study), years							
median	5.0		3.0		4.0		0.530[1]
minimum	0.0		1.0		2.0		
maximum	37.0		21.0		18.0		
lower quartile	2.0		2.0		2.0		
upper quartile	7.0		8.0		7.5		
Mean deviation	5.53		4.45		4.44		
CV, %	98.33		89.07		78.7		
Number of recurrences in the 12 months before randomization							
mean	1.28		1.28		1.21		0.883[1]
95% CI, lower limit	1.15		1.12		1.05		
95% CI, upper limit	1.40		1.44		1.38		
Mean deviation	0.49		0.64		0.42		
CV, %	38.13		49.73		34.41		
Total number of recurrences							
median	3.0		3.0		3.0		0.090[1]
minimum	2.0		1.0		2.0		
maximum	12.0		10.0		10.0		
lower quartile	2.0		2.0		3.0		
upper quartile	4.0		4.0		4.5		
Mean deviation	1.94		1.75		1.91		
CV, %	56.26		52.75		48.29		
History of hormone therapy							
Number of patients receiving hormone therapy	abs.	%	abs.	%	abs.	%	
	48	78.69	50	81.97	23	82.14	0.878[2]

[1] Kruskal-Wallis test; [2] Pearson χ^2 test with Yates correction.

The characteristics of the groups of patients included in the efficacy analysis are shown in Table 1.

The mean durations of the main disease (from the moment of onset of first symptoms to the date of recruitment into the clinical study and signing of informed consent) in the groups of patients included in the efficacy analysis were 5.62 years in group 1, 5.0 years in group 2, and 5.64 years in group 3 (differences insignificant, $p = 0.53$).

Results and Discussion. During the study, the exacerbation frequency during the observation year was low, with mean values (per patient per year) of 0.18 in the glatiramer acetate groups (analysis of total number of exacerbations). This value was three times smaller than the value reported in the registration study of GA (0.59) [4], which is evidence for inclusion of sufficiently preserved patients with slow disease progression.

The efficacy of the treatment of RMS is known to be reflected not only by exacerbations, but also by the dynamics of changes on MRI scans. Assessment of MRI in terms of the CUA (total of the number of new contrast-accumulating foci on T1 MRI scans and new foci on T2 scans or cases of increases in foci on T2 scans without double counting) and assessment of key MRI parameters (number of contrast-accumulating foci in the T1 regime; number of new or enlarged foci in the T2 regime; changes in the volume of foci in the T2 regime; changes in the volume of hypointense

TABLE 2. Dynamics of Main MRI Measures

MRI parameters	BCD-063	Copaxone-Teva	Placebo
CUA			
from screening to week 24	3.81 (4.95)	2.59 (3.55)	2.23 (2.84)
from week 24 to week 48	0.89 (1.43)	1.06 (1.69)	2.71 (3.3)
Number of T1 Gd^+ foci			
screening period	2.0 (2.49)	1.45 (2.45)	1.91 (3.31)
week 48	0.49 (1.12)	0.26 (0.57)	1.24 (2.53)
Number of new T2 foci			
week 24	2.31 (3.19)	1.49 (2.66)	1.45 (2.18)
week 48	0.40 (0.69)	0.66 (1.29)	2.0 (2.43)
Volume of T2 foci			
screening period	6.18 (6.82)	4.06 (4.67)	4.0 (4.08)
week 24	6.73 (7.29)	4.21 (4.61)	4.39 (3.9)
week 48	6.33 (6.97)	3.99 (3.95)	4.58 (4.44)

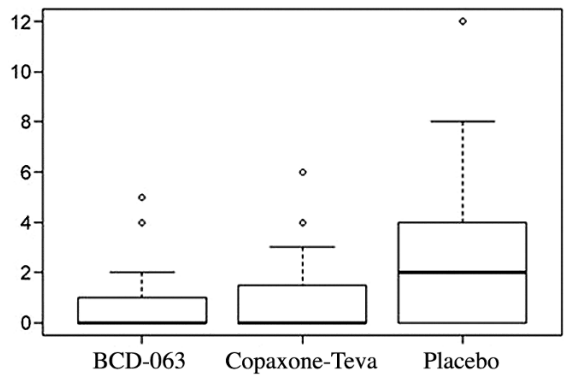

Fig. 1. Assessment of overall numbers of new contrast-accumulating foci on T1 MRI scans and new foci on T2 scans or cases of enlarged foci on T2 scans without double counting at week 48 in the different treatment groups.

foci on T1 scans demonstrated the absence of any difference in the efficacies of BCD-063 and Copaxone-Teva (Fig. 1).

CUA at 48 weeks was 0 [0; 1.0] in the BCD-063 group, 0 [0; 1.5] in the Copaxone-Teva group, and 2 [0, 4.0] in the placebo group (p = 0.0449). Pairwise comparison of the BCD-063 group and the Copaxone-Teva group at week 48 gave p = 1.0, which is evidence for the absence of any differences in efficacy in terms of this measure between the study formulation and reference preparation.

Changes in CUA over time (Table 2) were statistically significantly both in the BCD-063 group and the Copaxone-Teva group (p = 0.000034 and p = 0.002547 (paired Wilcoxon test), respectively. In the placebo group there was no statistically significant change in this parameter over time (p = 0.1528, paired Wilcoxon test). These results provide evidence of a significant decrease in MRI activity in terms of CUA at the visit at 48 weeks in the GA groups and the absence of any effect in the placebo group.

Given that MRI is one of the most sensitive methods for identifying changes in the course of illness and CUA reflects the overall assessment of new and enlarged foci and is a complex indicator characterizing the dynamics of pathological changes in the CNS, the results obtained here lead to the conclusion that there were no differences between the efficacies of BCD-063 and Copaxone-Teva and that there were significant differences between the efficacies of BCD-063 and placebo.

The number of contrast-accumulating foci on T1 scans at 48 weeks (Fig. 2) of treatment decreased statistically significantly in both the BCD-063 and reference agent groups (p = 0.00114 and p = 0.00036, respectively, Friedman's test), with no statistically significant dynamic in the placebo group (p = 0.21157). These data demonstrate the equivalence of the efficacies of GA from Biocad and Copaxone-Teva.

There were no statistically significant differences in the numbers of new foci on T2 scans at 24 weeks in all three groups (p = 0.3874, Kruskal–Wallis test). There were no significant differences in the number of new foci on T2 scans at 48 weeks between test formulation and reference agent (p = 1.0, Wilcoxon test), while statistically significant differences were seen between the GA and placebo groups. Changes in this measure over time were statistically significant in the GA groups (Wilcoxon test, p = 0.00002 in the BCD-063 group and p = 0.024 in the Copaxone-Teva group).

TABLE 3. Patients with Exacerbations and Numbers of Exacerbations during the Observation Year in Patients by Treatment Group (the mITT population)

Exacerbations per year	BCD-063 group (n = 61)		Copaxone-Teva group (n = 61)		Placebo group (n = 28)	
	number of patients	number of exacerbations	number of patients	number of exacerbations	number of patients	number of exacerbations
MRI-confirmed exacerbations	1	1	1	1	1	1
	1	1	1	1	1	1
	1	1	1	2	1	1
	1	2	1	1	1	1
	1	1	1	1	1	1
Total in group	5 (8.2%)	6	5 (8.2%)	6	5 (17.9%)	5
Exacerbations not confirmed by MRI	1	1	1	1	1	1
	1	1	1	1	1	1
	1	1	1	1		
	1	1	1	1		
	1	1	1	1		
Total in group	5	5	4*	5	2	2
All exacerbations in group	10 (16.4%)	11	9 (14.8%)	11	7 (25.0%)	7

*One patient of this group experienced two exacerbations during the year, one confirmed by MRI, not confirmed by MRI. This patient was recorded in the group with MRI-confirmed exacerbations.

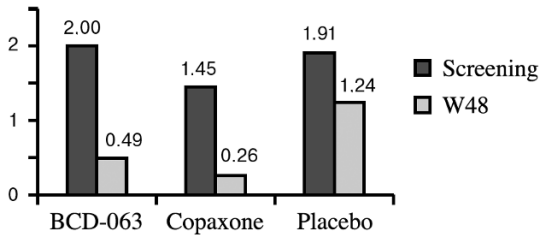

Fig. 2. Number of Gd-accumulating foci in T1 scans at screening and at treatment week 48.

There were no statistically significant differences in the numbers of enlarged foci on T2 scans between the BCD-063 and Copaxone-Teva groups at either 24 or 48 weeks.

Assessment of changes in focus volume on T2 scans showed some increase in this indicator at 24 weeks in all groups, though without any statistically significant differences between groups or between visits within a group. At assessment at treatment week 48, there were improvements consisting of reductions in mean focus volume in the GA groups, with a statistically significant change in the BCD-063 group (p = 0.04741, Friedman test) but no significant difference in the Copaxone-Teva group (p = 0.12308, Friedman test). The placebo group showed a statistically significant increase in this indicator over time (p = 0.00079, Friedman test), reflecting deterioration in the course of illness.

Thus, the overall MRI results at treatment week 48 lead to the conclusion that there is no difference between the efficacies of BCD-063 and reference agent Copaxone-Teva.

Assessment of the numbers of MRI-confirmed exacerbations per patient per year showed that the mean number of exacerbations in the BCD-063 (Biocad, Russia) group was (mean, standard deviation) 0.098361 (0.351422), compared with 0.098361 (0.351422) in the Copaxone-Teva group; there was an almost two-fold difference in this indicator in the placebo group, at 0.178571 (0.390021).

Of the 150 patients included in the efficacy analysis, MRI-confirmed exacerbations were seen during the observation year in 15 patients (five patients in each treatment group). Considering that some patients had more than one exacerbation during the observation period, the total number of exacerbations during the year was 17, of which six were in the BCD-063 group, six were in the in the Copaxone-Teva group, and five cases were in the placebo group. Exacerbations not confirmed by MRI were recorded in a further five patients in the BCD-063 group, four in the Copaxone-Teva group, and two in the placebo group. Table 3 shows all exacerbations in the groups, both confirmed and not confirmed by MRI scans.

An additional indicator confirming the similar efficacies of the formulations was the odds ratio for the development of exacerbations in the BCD-063 and Copaxone-Teva groups, which was 1.0, indicating that there was no statistically significant difference in efficacy between treatment

TABLE 4. Overall Safety Data, Results at 48 Weeks of Treatment with Glatiramer Acetate

AE	BCD-063 group (n = 61)		Copaxone-Teva group (n = 63)		Placebo group (n = 31)		p^1
	abs.	%	abs.	%	abs.	%	
Any AE (including SAE)	39	63.93	39	61.91	15	48.39	0.345
Treatment-related AE/SAE	20	32.79	23	36.51	4	12.90	0.044[2]
							$p_{1,2}$ = 0.708
							$p_{1,3}$ = 0.047
							$p_{2,3}$ = 0.028
Grade 3–4 AE	5	8.20	3	4.76	0	0.00	0.285
Grade 3–4 treatment-related AE	2	3.28	0	0.00	0	0.00	0.192
Any SAE	5	8.20	3	4.76	1	3.23	0.944
Treatment-linked SAE	2	3.28	0	0.00	0	0.00	0.192
All cases of premature termination of the study linked and not linked with AE/SAE	7	11.48	8	12.70	4	12.90	0.896
Treatment withdrawal (total frequency)	3	4.92	1	1.59	0	0.00	0.427
Treatment withdrawal (drug-linked)	1	1.64	1	1.59	0	0.00	1.00
Lethal outcomes	0	0.00	0	0.00	0	0.00	1.00

[1]Fisher's exact test for multiple groups; [2]statistically significant differences in this case by pairwise comparison of groups and using the two-tailed Fisher's exact test/Pearson's χ^2 test with Yates correction, $p_{1,2}$ – comparison of study formulation and reference agent groups; $p_{1,3}$ – comparison of study formulation and placebo groups; $p_{2,3}$ – comparison of reference formulation and placebo.

groups. The odds ratio for the BCD-063 and placebo groups was 0.410. This means that the chance of developing an exacerbation was 41% higher in the placebo group than in the study formulation group.

Thus, efficacy of treatment with GA BCD-063 was confirmed both on the basis of the most sensitive indicator, CUA, and in terms of the frequency of exacerbations.

The most sensitive endpoint evidencing the superiority of study formulation and reference preparation over placebo consisted of changes in MRI measures, as this reflects the pathological substrate of the course of MS and, thus, the direct actions of the formulations. CUA reflects the overall assessment of new and enlarged foci and is a complex indicator characterizing the dynamics of pathological changes in the CNS, such that analysis of this indicator leads to the confident conclusion that there is no difference between the efficacies of study formulation and reference agent Copaxone-Teva and that there are differences in the efficacies of the two GA formulations compared with placebo. Thus, differences in CUA between the GA and placebo groups were statistically significant (p = 0.0449) by the end of one year of treatment within the framework of this study.

As for any other formulation, efficacy is not the only important factor – safety in patients with MS is also important. Furthermore, systemic adverse events (AE) and the development of local AE both play an important role in the compliance of patients with MS. Both study agent BCD-063 and reference formulation Copaxone-Teva demonstrated favorable safety profiles.

Overall data on safety results are shown in Table 4.

The commonest AE in the present study were local reactions, which were recorded in 19 patients (31.15%) in the test formulation group, 16 patients (25.40%) in the reference agent group, and three patients (9.86%) in the placebo group ($p > 0.05$). Local reactions consisted of erythema, pain, itch, burning sensations, irritation, numbness, and hardness at administration sites, along with local hyperthermia (or different combinations of these symptoms). In general, all the local reactions recorded were of severity grade 1; local reactions of grade 2 were rarer. Severe local reactions were not seen. Comparison of the frequencies of grade 1 and 2 local reactions between the GA groups revealed no statistically significant differences ($p > 0.05$).

Of the SAE recorded in the present study, some were felt by the investigators to be related to the study treatment and were expected in patients receiving GA. This group of AE consisted of acute gastroenteritis and Quincke's edema. Considering their uniform nature, these events did not alter views as to the safety of GA produced by Biocad.

Comparison of the frequencies of detection of individual AE revealed no significant differences in the vast majority of cases. The AE noted in this study and assessed by the investigators as GA-related in the framework of this investigation were mainly expected, as they have been seen

in previous clinical studies using an analogous dosing regime with Copaxone-Teva. Significant differences in the incidence of AE were seen between the GA groups and the placebo group in relation to treatment-related AE, which was expected, though severe drug-associated AE showed no statistically significant differences between the GA and placebo groups. There were no lethal outcomes during treatment in the GA groups.

These data indicate that BCD-063 has a favorable safety profile and in terms of this parameter is comparable with Copaxone-Teva.

Conclusions. The results obtained here provide evidence of the therapeutic equivalence and safety of Timexon (BCD-063, Biocad, Russia) and reference agent Copaxone-Teva.

The registration number of this trial at ClinicalTrials.gov was NCT02753088.

Conflicts of interests: R. A. Ivanov and M. S. Shustova are employees of Biocad.

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