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Colostrinin[1] (a naturally occurring, proline-rich, polypeptide mixture) in the treatment of Alzheimer's disease

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Abstract. This study was designed to confirm or negate findings from earlier trials demonstrating that Colostrinin, a novel compound derived from ewes' colostrum, has potential in the treatment of mild or moderate Alzheimer's Disease (AD). 105 patients were recruited from six psychiatric centres in Poland. The trial consisted of a 15 week double-blind phase comparing Colostrinin with placebo, followed by a second 15 week open labelled phase when all patients received Colostrinin. The dosage of Colostrinin was 100 μg on alternate days for three weeks followed by two weeks drug-free. This cycle was repeated three times for each phase. The primary outcome measures used were Alzheimer's Disease Assessment Scale-cognitive portion (ADAS-cog) and Clinical Global Impression of Change (CGIC). Secondary outcome measures were Instrumental Activities of Daily Living (IADL); Mini-Mental State Examination (MMSE); ADAS-non cognitive test (ADAS-non cog); and overall Patient Response. The main outcome measures were assessed at week 15 when active was compared with placebo but all parameters were evaluated at baseline, week 15 and week 30. Two separate statistical analyses were undertaken, a Full Sample Analysis (FSA) in which all missing values were replaced with the worst result observed and a Valid for Efficacy (VFE) analysis in which those patients who had serious protocol violations were excluded. This resulted in 14 patients being excluded from the VFE-analysis. The FSA analysis at week 15 showed a stabilizing effect of Colostrinin on cognitive function in ADAS-cog ($p = 0.02$) and on daily function in IADL ($p = 0.02$). The overall patient response was also in favour of the active ($p = 0.03$). Patients graded as mild on entry also showed a superior response of ADAS-cog compared with more advanced cases ($p = 0.01$). Evidence from this study indicates an early beneficial effect on cognitive symptoms and daily function. Colostrinin has potential value in the treatment AD.

Keywords: Colostrinin, proline-rich polypeptide (PRP), Alzheimer's Disease (AD), cognitive function, efficacy parameters, full statistical analysis (FSA), valid for efficacy (VFE)

1. Introduction

The search for effective therapies to cure or prevent AD continues unabated but so far none have proven successful. Treatments for AD follow two strategies. One approach is to treat the disorder symptomatically whilst the other is aimed at a primary cure or prevention by disease-modification. Examples of the first type are cholinesterase inhibitors (ChEI) which improve cognitive function.

To date, no compounds have been approved in the disease-modifying category but a variety of biological agents (e.g. antioxidants, anti-inflammatories, oestrogens, secretase inhibitors and certain immunological agents) are of interest. Colostrinin potentially falls into the latter group because of its putative actions on cytokine induction [4,6] and amyloid ß plaque formation [2]. It also modulates T-cell activity and inhibits humoral antibody formation [5].

AD is associated with signs of progressive cogni-

[1]Colostrinin is the registered trade name for a proline-rich polypeptide mixture (PRP) derived from ovine colostrum.

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tive impairment i.e. loss of intellectual ability sufficient to interfere with a person's daily activities, social life and occupational performance. Reasoning, memory (particularly the ability to retain new information) and language function are all affected leading to disturbances in executive function (i.e. planning, organizing, sequencing and abstract conceptualisation). Individual changes in each of these cognitive functions (as measured in this study) are used as longitudinal measures of improvement or deterioration.

Both the incidence and prevalence of AD is increasing worldwide as people live longer. For example, the prevalence of dementia (mostly AD) increases from one percent of the population in their early sixties to 25–50 percent in their late eighties. Moreover, the number of cases reported in different countries varies considerably. The United Kingdom appears to have the highest incidence and prevalence amongst the developed countries (2–3 times that of the USA and 3–4 times that of Japan). This may be partly explained on grounds of better diagnosis and higher reporting rates in the U.K., although differences in genetic, dietary or environmental factors are probably more important.

Whilst the symptomatic treatment of cognitive dysfunction with ChEI is of great value in temporarily improving memory and quality of life, there is need for a primary treatment strategy aimed at modifying the disease process from the earliest stage (i.e. at the first signs of cognitive impairment or even before symptoms begin to appear) in an effort to slow down clinical deterioration. Such an approach would require treatments that are safe and free from unpleasant side effects as they would need to be taken prophylactically by otherwise healthy elderly who may be at risk from developing AD merely because of their increasing age and/or genetic predisposition.

Colostrinin is a naturally occurring proline-rich polypeptide mixture extracted from ovine colostrum as described by Janusz et al. 1981. It has been tentatively classified as an immunomodulator. It is bioavailable in humans after oral absorption of 50–200 μg and pilot studies have shown improvement in cognitive and behavioural abilities of AD patients [9]. The purpose of this study was to confirm its positive effects on cognitive function and monitor its safety profile.

2. Materials and methods

2.1. Patient population

Eligible patients were 50 years of age and over suffering from probable AD as defined in the fourth edition of the DSM-1V (Diagnostic and Statistical Manual 1V) and NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke, AD and Related Disorders Association). Mildly or moderately affected patients only were admitted to the study as measured on the MMSE i.e. 10 to 24 points inclusive. Only ambulatory patients able to attend the clinic accompanied by a relative or caregiver were enlisted, either of whom could provide written, informed consent. Patients with severe somatic disorders, especially those likely to be associated with dementia, were excluded e.g. cerebrovascular disease (Hachinski ischaemic score > 6), endocrine disorders, Parkinson's Disease, psychoses, schizophrenia and severe affective disorders. Evidence of neurological abnormalities on recent brain scans (other than those changes expected with probable AD) excluded the patient from the trial. The study was planned and conducted in strict accordance with Polish law and licensed to proceed by the Central Register of Clinical Trials in Warsaw. The study procedures followed were in accord with the ethical standards of the institutional committees on human experimentation and with the Helsinki Declaration (Somerset West Amendment 1996) and the ICH Guideline for Good Clinical Practice (ICH-GCP).

2.2. Study design

This was a multicentre trial consisting of a placebo-controlled, double-blind treatment for 15 weeks (Phase 1) followed by 15 weeks open – label during which all patients received active therapy (Phase 2). Phase 1 was designed to evaluate the efficacy of Colostrinin compared with placebo in mild to moderately severe cases of probable AD. Phase 2 looked at long term tolerability and sustained efficacy of Colostrinin. All patients were outpatients and were examined and assessed by a consultant psychiatrist and a qualified psychologist experienced in psychometric testing. Six hospital neurological/psychiatric centres in Poland, namely Bydgoszcz, Gdansk, Katowice, Lodz, Lublin and Torun were involved.

Patients with a diagnosis of probable AD were recruited from the outpatient departments of the centres involved. Those meeting the strict entry criteria were randomised into equal groups to receive either Colostrinin or placebo. The randomization programme was provided by the Biometric and Medical Documentation Department of the University of Ulm. Sealed codes were stored by the head of department at Ulm with one copy for the manufacturer of the trial

Table 1
Difference in ADAS-cog scores week 15 minus week 0 (FSA - missing values replaced)

	N	Minimum	Median	Maximum	Mean
TREATMENT					
Colostrinin	24	−14	−0.2	15	0.5
Placebo	21	−11	5.7	16	5.3
TOTAL	45	−14	2.0	16	2.8

The result of the exact Wilcoxon-rank sum test comparing the differences in ADAS-cog scores between Colostrinin and placebo at the interim analysis (FSA-missing values replaced) was:

unstratified $p = 0.0212$

stratified by hospital centre $p = 0.0216$

The results of the corresponding VFE analysis (i.e. missing values *not* replaced) performed on data from 42 patients were:

unstratified $p = 0.0909$

stratified $p = 0.0951$

The conditional power was calculated for both interim results according to Lan and Wittes (Biometrics 1988). The probability of a statistically significant result being achieved at final analysis with $40 + 40 = 80$ total patients, (one sided hypothesis and a local significance level of 0.020) was 83% on FSA reducing to 37% on VFE.

Table 2
Differences in ADAS-cog scores week 15 minus week 0 (FSA-missing values replaced)

	N	Minimum	Median	Maximum	Mean
TREATMENT					
Colostrinin	53	−14.00	0.33	19.99	2.05
Placebo	52	−10.67	4.67	19.99	5.36
TOTAL	105	−14.00	2.00	19.99	3.69

(Negative differences signify clinical improvement)

The median difference for Colostrinin was 0.33 and therefore lower than the median difference of 4.67 for placebo. The Wilcoxon rank sum test (SAS Version 8.1) showed a one-sided p value of 0.02. Additionally, 95% confidence intervals ranged from −1.00 to 2.55 for Colostrinin and from 2.00 to 7.00 for placebo. The stratified Wilcoxon rank sum test comparing results from six centres also yielded a one-sided p value of 0.02.

supplies (UNIA) and a further copy going to the responsible biometrician in Poland. Only authorized personnel of UNIA or the biometrician had access to the randomization codes so ensuring that the sponsor, investigators, trial managers and monitors all remained blinded. Sealed envelopes were provided for each patient to allow access to an individual patient's randomization code in the event of a medical emergency. Strict procedures were adopted for recording such an event.

2.3. Dosage regimen

The Colostrinin treatment group received tablets containing 100 μg of active substance plus excipients (mannitol, magnesium stearate and sodium chloride). The placebo patients received identical tablets except for the active ingredient. Patients allocated to the Colostrinin group received one active tablet on alternate days (i.e days 1, 3, 5 etc.) interspersed with a placebo tablet on the even days. This regimen was administered for three weeks followed by two weeks treatment on daily placebo only. Patients in the control group received one placebo tablet daily throughout the five week period. The complete five week cycle was repeated three times throughout Phase 1.

2.4. Compliance

Treatment compliance was measured every five weeks by checking the number of tablets dispensed, taken, returned and missing. Patients who took at least one day of medication were included in the full sample analysis (FSA).

2.5. Outcome measures

These were chosen with reference to the CPMP Note for Guidance in the Treatment of AD (CPMP/EWP/553 /95). Improvements were assessed in the following three domains: cognitive (memory, language and reasoning); functional (activities of daily living); and global (overall clinical progress including assessment

of mental status). The primary endpoints chosen were ADAS-cog [13] and CGIC [3]. The secondary endpoints included IADL [10]; MMSE [1]; Global Deterioration Scale [12]; Geriatric Depression Scale [14]; ADAS-non cog [13] and Gradation of Overall Patient Response. Finally ADAS-cog was used for subgroup analyses for patients with different severity of AD. Outcome parameters were evaluated at baseline, weeks 15 and 30. ADAS-cog and CGIC were assessed by different physicians.

3. Safety

3.1. All adverse events were recorded at each visit

3.1.1. Statistical analysis

The method of handling patient data and details of statistical analysis to be employed were determined in the study protocol and all primary evaluations were carried out on blinded data. An interim analysis was undertaken after 46 patients had completed the 15 weeks double-blind phase (Phase 1) to determine whether or not the study should continue. The principal outcome evaluation was planned on completion of Phase 1 by at least 90 patients. A third evaluation was planned at the end of the open Phase 2 which focused on safety and tolerability.

For the primary outcome measures a one-sided exact Wilcoxon rank sum test was adopted at a total level of significance of 0.025.This level of significance was divided into two nominal levels, namely, 0.005 for the interim analysis and 0.02 for the final evaluation. For the interim analysis of efficacy, ADAS-cog was the only primary outcome variable used whilst the two primary outcome variables ADAS-cog and CGIC were used for the final evaluation of short term efficacy (15 weeks of Phase 1) as well as longer term outcome (30 weeks of Phase 1 and 2 together). The two primary outcome variables were tested as a priori ordered hypotheses: first ADAS-cog, second CGIC. If the test on ADAS-cog was positive then CGIC was tested also. If ADAS-cog was not significant (NS) then by definition, neither was CGIC.

The statistical plan adopted for handling patient data for analysis prior to unblinding consisted of a Full Sample Analysis (FSA) in which all patients were included for outcome analysis if they had received at least one dose of trial medication, their missing values being replaced with the worst result observed amongst all patients analysed. In addition, a Valid for Efficacy (VFE) analysis was performed on the primary outcome variables (ADAS-cog and GCIC) as well as the secondary outcome variable IADL if less than 90% patients in the FSA were valid for efficacy (i.e. more than 10% patients had missing outcome data).

4. Results

4.1. Interim analysis

This was undertaken on the first 46 patients completing the 15 weeks double-blind Phase 1. The purpose of this analysis was to identify a superiority of Colostrinin over control so that the trial could be terminated early if a local significance of 0.005 was attained on the ADAS-cog using the one-sided exact Wilcoxon rank sum test. The International Steering Committee (ISC) examined blinded data only when deciding on patient eligibility for inclusion in the interim analysis. One patient was excluded from analysis by the Committee due to erroneous reception of active drug right from the beginning, leaving 45 patients for efficacy analysis by FSA. A further three patients were excluded from the VFE due to discontinuation of therapy before 15 weeks (2 patients) and lack of cooperation (1 patient).

The median age of the patients from the interim analysis was 72.1 years and roughly two-thirds were women. There were three more patients in the Colostrinin than in the placebo group but overall the two groups were comparable. The baseline scores for the primary outcome variable ADAS-cog were not remarkably different for active and placebo.

The changes in ADAS-cog scores at week 15 compared with baseline are shown in Table 1.

Whilst the interim analysis demonstrated a clear trend for efficacy in favour of Colostrinin on the basis of the ADAS-cog results, the local level of significance of 0.005 as specified in the protocol was not reached. However, the probability of attaining a statistically significant result on completion of Phase 1 was considered to be quite good so the ISC recommended to continue the trial but with an additional number of 18 patients enrolled to facilitate an increase of power. Hence, the original planned 90 patients (45 in each group) was increased to 108 patients (54 in each group).

There were no safety concerns at this stage to influence this decision.

Table 3
Differences in median IADL scores weeks 15 minus week 0 (FSA – missing values replaced)

	N	Minimum	Median	Maximum	Mean
Treatment					
Colostrinin	53	−11.00	0.00	8.00	0.38
Placebo	52	−7.00	2.00	8.00	1.98
TOTAL	105	−11.00	1.00	8.00	1.17
95% C.I. (for median IADL differences) was 0 to1 for Colostrinin and 1 to 3 for placebo Explorative Wilcoxon one-sided p value = 0.02. Explorative stratified Wilcoxon exact one-sided p value = 0.02					

Table 4
Differences in median MMSE scores week 15 minus week 0 (FSA -missing values replaced)

	N	Minimum	Median	Maximum	Mean
Treatment					
Colostrinin	53	−16.00	0.00	6.00	−0.77
Placebo	52	−16.00	0.00	4.00	−2.60
TOTAL	105	−16.00	0.00	6.00	−1.68
95% C.I. (for median MMSE differences) was −1 to +2 for Colostrinin and −2 to +1 for placebo. Explorative Wilcoxon one-sided p value = 0.10. Explorative stratified Wilcoxon exact one-sided p value = 0.09.					

Table 5
Gradation of Overall Response

	Colostrinin	Placebo	Total
Deterioration	32	41	73
Stabilization (grade 1 but not grade 2 response)	15	7	22
Improvement (grade 2 response)	6	4	10
Total patients	53	52	105
Explorative Wilcoxon one-sided exact p value = 0.03			

5. Main analysis

5.1. Primary efficacy parameters

The first test postulated that the median difference in ADAS-cog scores (week 15 minus baseline) would be lower in the Colostrinin group than in the placebo group. (Local level of significance = 0.020 as this variable had already been tested in the interim analysis). The results are shown in Table 2.

In view of the statistical significance obtained in the ADAS-cog analysis the next test of significance was performed on the second primary efficacy parameter (CGIC). The CGIC which measured the individual doctor's global impression of the patient's clinical progress on a scale of one to seven failed to record any significant changes in either treatment group throughout the entire study period. It seemed likely that this test, although chosen as a primary parameter, was not sufficiently sensitive to measure clinical progress over such a relatively short period of time.

5.2. Secondary efficacy parameters and subgroup analyses

Amongst the tested secondary outcome variables were IADL, MMSE, Global Deterioration Scale (G.Det.S), Geriatric Depression Scale (G.Dep.S), AD AS-noncog and Gradation of Overall Patient Response. ADAS-cog Differences Stratified for Clinical Severity were investigated in the ensuing subgroup analyses.

5.3. IADL

This test measured the functional ability of patients in relation to activities of daily living such as shopping and house-keeping on a scale of 8 to 31 (severe impairment). At week 15 the median IADL score remained unchanged from baseline in the Colostrinin group whilst it increased (worsened) by two points on placebo (Table 3).

5.4. MMSE

This is a short test used to measure cognitive function but in less detail (i.e. less sensitive) than the ADAS-

Table 7
Differences in ADAS-cog scores week 15 minus week 0 stratified according to mild or moderate severity at baseline

		N	Minimum	Median	Maximum	Mean
Mild	Colostrinin	29	−14	0.00	19.99	0.28
	Placebo	33	−8.34	3.66	19.99	4.99
	Total patients	62	−14	1.01	19.99	2.78
Moderate	Colostrinin	24	−10.00	4.00	19.99	4.19
	Placebo	19	−10.67	6.34	19.99	6.02
	Total patients	43	−10.67	5.67	19.99	5.00
Explorative stratified Wilcoxon (StatXact) – one-sided exact p value = 0.01						

Table 6
Distribution of patients according to mild or moderate disease severity on entry

	Colostrinin	Placebo	Total
Mild	29	33	62
Moderate	24	19	43
Total patients	53	52	105

cog. It is not diagnostic of AD but is useful in plotting changes in cognitive function especially in the domains of orientation, registration, calculation, attention, recall and language. The scores range from zero to 30 (best) so a positive difference signifies improvement. (Table 4).

5.5. ADAS-non cog

ADAS consists of two parts, a test of primary cognitive function (memory, language and praxis) and a secondary test of non-cognitive function (mood state and behavioural disturbance). There were 10 assessments in the non-cognitive test with a score ranging from zero to 50 (severe impairment). A very slight deterioration of <1 unit was seen in the median differences between week 15 minus week 0 for both treatment groups. The Wilcoxon test produced a one-sided p value $= 0.16$ and the 95% C.I. ranged from -2 to $+2$ for Colostrinin and from 0 to 3 for placebo.

5.6. Overall response

An overall benefit of Colostrinin was calculated in line with the recommendations of the CPMP (Note for the Guidance of Medical Products in the Treatment of AD). The following criteria were determined in the study protocol:

Grade 1 response was defined as a stabilization (i.e. no deterioration) of ADAS-cog, CGIC and IADL at week 15.

Grade 2 response was defined as an improvement of four or more points on the ADAS-cog scale together with no relevant deterioration of CGIC and IADL.

Thus for the overall response, patients were divided into grade 1 (stabilization), grade 2 (improvement) or negative response (deterioration). See Table 5.

5.7. Subgroup analysis

A subset analysis was performed on patients classified according to their degree of cognitive impairment on entry into the study.

Mild- MMSE score at baseline of 17 to 24

Moderate- MMSE score at baseline of 10 to 16

See Table 6.

The differential responses in ADAS-cog of patients stratified according to mild or moderate severity was calculated (Table 7).

6. Double-blind (phase 1) valid for efficacy (VFE) analysis

It was specified in the protocol that a VFE analysis would be undertaken in addition to the FSA if less than 90 percent of patients had complete and verifiable data. Fourteen patients (13%) were considered not valid for efficacy leaving the VFE analysis to be performed on 91 patients. Ten of the patients excluded were in the placebo group. Thus, the one-sided tests based on the 91 patients VFE were considered to be of an exploratory nature only with a significance level of 2.5% ($= 0.025$). The ADAS-cog results for VFE are shown in Table 8.

6.1. Subgroup analysis

Finally, a VFE analysis was performed on patients stratified for severity of disease on entry as in the main FSA. Unlike the FSA where the differences were highly statistically significant, the differences in median scores failed to reach significance at < 0.025 although the mild cases showed improvement in the median scores over 15 weeks on Colostrinin compared with a deterioration with placebo (-0.33 for Colostrinin versus 2.00 for placebo).

Table 8
Differences in ADAS-cog scores week 15 minus week 0 (VFE- missing values not replaced)

	N	Minimum	Median	Maximum	Mean
TREATMENT					
Colostrinin	49	−14.00	0.00	15.34	1.38
Placebo	42	−10.67	2.50	15.67	2.52
TOTAL	91	−14.00	1.33	15.67	1.90

Explorative Wilcoxon rank sum one-sided p value = 0.17 95% C.I. (median ADAS-cog differences) was −1.66 to 2.00 for Colostrinin and +1.01 to 6.00 for placebo.

Table 9
Overall Response after 30 weeks (phases 1&2)

	15weeks	30weeks
Group 1 (active + active)		
Deterioration	30	35
Stabilization (grade1 but not grade 2 response)	16	9
Improvement (grade 2 response)	6	8
Total patients	52	52
	15 weeks	30 weeks
Group 2 (placebo + active)		
Deterioration	33	34
Stabilization (grade 1 but not grade 2 response)	6	6
Improvement (grade 2 response)	4	3
Total patients	43	43

6.2. FSA versus VFE

The differing results of the FSA and VFE analysis are due to the 14 patients not valid for efficacy. Nine out of the 14 patients were excluded from VFE because of missing ADAS-cog values. It is assumed that the loss of this data (7 placebo and only 2 active) was responsible for the VFE analysis leading to a worse result than the FSA by reducing the statistical sensitivity of the test. This was anticipated to some extent at the interim analysis when the conditional power was calculated as an 83% probability of attaining ($p = 0.02$) statistical significance on FSA reducing to only 37% on VFE.

7. Open label (Phase 2)

Patients who completed the double-blind Phase 1 proceeded to Phase 2 where they were all treated with Colostrinin using the same dosage regimen as in the colostrinin group of Phase 1 but in open label.

For the purpose of statistical analysis patients were divided into Group 1 (i.e. those on active therapy during Phase 1&2) and Group 2 (i.e. those on placebo during Phase 1 and active Phase 2. The total sample of patients of the open label phase consisted of 95 patients, 52 in Group 1 and 43 in Group 2. Subsequent analyses are based on the open-label sample.

Changes in the median values of ADAS-cog throughout the 30 week study are shown in Fig. 1.

Progression of ADAS-cog scores in Group 1 during Phase 1 was similar to progression in Group 2 during Phase 2 (Fig. 2). In both groups, the mentioned intervals are the first 15 weeks of active treatment. Hence, the degree of response in terms of ADAS-cog score during the first 15 weeks of Colostrinin treatment was remarkably similar in both groups.

The overall response is shown in Table 9.

This suggests that the stabilization and overall improvement (compared with baseline) seen in 22 of the Group 1 patients during double-blind Phase 1 is reduced to 17 at week 30. In Group 2 only one additional patient deteriorated further during Phase 2 possibly indicating a slowing down of symptomatic progression following the delayed introduction of Colostrinin.

A similar effect was seen with MMSE where the median scores for Group 1 remained stable at week 15 and slightly improved at week 30 whilst for Group 2 they deteriorated by three points during Phase 1 (placebo) and then remained stable.

7.1. Subgroup analysis

A subgroup analysis of ADAS-cog was performed at 30 weeks using the same classifications as for the main evaluation at week 15 (Table 6). Patients classified as *mild in Group 1* remained stable on ADAS-cog at week

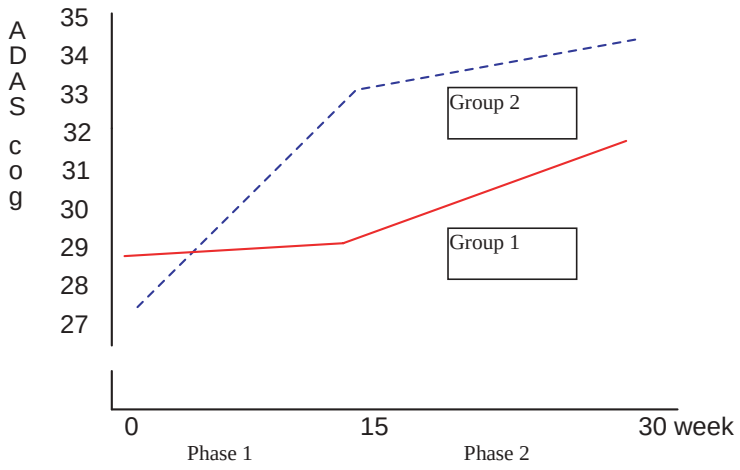

Fig. 1. ADAS-cog changes in median values over 30 weeks.

30 whereas the *moderately severe* cases showed a progressive increase (deterioration) in ADAS-cog scores (1.5 v 8.3). Group 2 patients showed a similar pattern.

8. Safety results

The incidence and nature of adverse events reported were similar in both the active and placebo groups. Generally, the treatment was well tolerated and the relatively high drop-out rates due to side-effects associated with the ChEI were not encountered in this study.

9. Discussion

This study was designed to support or negate findings from earlier clinical trials suggesting that Colostrinin was effective in improving the symptoms of cognitive impairment in patients with mild to moderate AD. The statistical plan adopted for handling patient data prior to unblinding provided the most severe test of significance and was chosen to be on the safe side by underestimating the outcome.

The main efficacy analysis was performed on data from the first 15 week double-blind period (Phase 1) when Colostrinin was compared with placebo across several clinical parameters. Results showed that Colostrinin was significantly better than placebo in some but not all tests. Statistically significant differences ($p = 0.02$) were found in the primary efficacy parameter ADAS-cog and in the secondary variable IADL on the FSA. This advantage was reduced (i.e. not statistically significant) on VFE due to the loss of 14 patients to the analysis, ten of whom were on placebo. However, the trends with the VFE analysis remained in favour of Colostrinin and tended to support the beneficial effects found on FSA.

Thus, the effect on two major efficacy parameters (one measuring cognitive changes and the other functional changes in daily activities) proved favourable. However, CGIC (clinical global impression of change) showed no movement for either treatment group throughout the whole study suggesting that overall clinical changes may be more difficult to measure, at least in the short term, and should be reserved for long-term follow-up studies stretching over several years. Likewise, ADAS-non cog, which assesses mood and behavioural changes did not appear to be a very sensitive measure in the short term and contributed nothing to the results. The MMSE result was at variance with the ADAS-cog and IADL in so far as the difference between Colostrinin and placebo did not reach statistical significance ($p = 0.10$). However, recorded MMSE scores at weeks 15 were better for Colostrinin than placebo in all hospitals except the Bydgoszcs centre where the median MMSE difference (week 15 – week 0) for Colostrinin was equal to placebo. MMSE is a short, quick test which measures crude changes in cognitive function and, as such, is a much less sensitive test than ADAS-cog which was chosen as the primary parameter in this study.

The overall benefit analysis in the full sample showed 40% patients stabilized or improved on Colostrinin at week 15 as opposed to only 21% on placebo. This figure reduced to 33% on Colostrinin at week 30 (Group 1) but showed a stabilization of Group 2 when converted to Colostrinin during Phase 2. Finally, a subset

analysis showed that patients stratified as mild on entry responded much better ($p = 0.01$, FSA) than more advanced cases. This differential response between mild and moderate cases was maintained throughout the study and may be considered an important therapeutic finding if confirmed in future studies.

The implications of these results require elaboration. In view of the fundamental difference in the mode of action postulated for Colostrinin compared with symptomatic treatments like the ChEI, the effects on cognitive measurements are not directly comparable. For example, because the ChEI act by increasing presynaptic acetylcholine, a positive improvement in cognitive scores (especially memory) as measured by ADAS-cog and MMSE would be expected. However, Colostrinin has no direct action on acetylcholine but may help to sustain whatever level of acetylcholine function existed at the start of the study. *Thus, maintained levels of cognitive function over the period of the study compared with placebo may be most relevant whilst a similar finding with ChE inhibitors might be considered not significant. This appears to be the effect observed in this study*.

Early decline in AD is difficult to predict as there is considerable variability between individual patients but evidence from clinical trials suggests that, as a general guide, a normal elderly patient would expect to score zero points on the ADAS-cog (certainly less than five). In probable AD, an average annual decline of between 7 to 11 points on ADAS-cog can be expected in the earlier stages and accelerating as the disease progresses. Extrapolation from Tables 1&2 suggests that Colostrinin significantly slowed down the anticipated rate of decline during Phase 1 compared with the placebo group whose median rate of decline was much closer to the expected. Unfortunately, this situation was not fully maintained in Phase 2 although the rate of decline does slow down in Group 2 patients during Phase 2 (see Fig. 1).

The natural history of AD is one of gradual and progressive clinical deterioration but the speed of regression varies considerably from individual to individual. This makes it difficult to set parameters for outcome – e.g. lack of deterioration may be considered a good outcome for a "disease-modifying" drug but not for a symptomatic treatment. Longitudinal studies show that, after the initial clinical diagnosis of possible AD – i.e. in cases with signs of mild cognitive impairment (MCI), there is an average progression to probable AD of 12–15% cases annually [11]. A significant reduction in this rate of decline from MCI to probable AD would be of great benefit but may require the routine, long-term administration of safe and well tolerated therapies from the very earliest signs of cognitive impairment in otherwise healthy individuals. Proof of long-term activity in significantly slowing down the disease progression requires studies of very different design to the majority of studies conducted in AD to date, (including the present one), which have tended to look at the short-term effects on cognitive function only.

Finally, it is worth noting that an extremely small dose of Colostrinin was utilized in this study (a total of 6.6 mg per patient for Group 1 and 3.3 mg for Group 2) and the treatment regimen was unduly complicated. This programme was based on previously published studies where the original investigators were concerned about the possible problem of tachyphylaxis as determined by the agent's ability to suppress the secretion of gamma-interferon by peripheral leucocytes *in vivo* [9]. An identical dosage regimen was used in this study which was designed to support or refute the earlier findings. Yet, in spite of this conservatively small dosage regimen, the results have demonstrated statistically significant beneficial effects on cognitive function which, if verifiable, suggests that Colostrinin is biologically active and its potential value in the early treatment of AD merits further study.

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