European Medicines Agency

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London, 4 March 2010

WITHDRAWAL ASSESSMENT REPORT
FOR
Ethyl eicosapent soft gelatin capsules

International Nonproprietary Name (INN):
Ethyl-eicosapent

Procedure No. EMEA/H/C/1148

Day 120 List of Questions as adopted by the CHMP with all information of a commercially confidential nature deleted.

This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

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LIST OF ABBREVIATIONS

AA:	Arachidonic Acid
(S)AE:	(Serious) Adverse Event
AUC:	area under curve
BHT:	butylated hydroxytoluene
CGI	Clinical Global Impression
COX:	cyclooxygenase
CYP:	cytochrome P450
DHA:	docosahexaenoic acid
DPA:	docosapentaenoic acid
EFA:	essential fatty acid
EPA:	eicosapentaenoic acid
GC-MS:	gas chromatography-mass spectrometry
HD:	Huntington's disease
ICH:	International Conference on Harmonisation
INR:	international normalized ratio
ITT	Intent To Treat
LOCF	Last Observation Carried Forward
MMSE	Mini-Mental State Examination
MRI	Magnetic Resonance Imaging
NCA:	non-compartmental analysis
NRG:	Name Review Group
NSAID	Non Steroid Anti Inflammatory Drugs
PP	Per Protocol
PUFA:	polyunsaturated fatty acid
RBC:	red blood cell
SIENA	Structural Image Evaluation, using Normalisation, of Atrophy
TMS	Total Motor Score
UHDRS	Unified Huntington's Disease Rating Scale

I. RECOMMENDATION

Based on the CHMP review of the data on quality, safety and efficacy, the CHMP considers that the application for Ethyl Eicosapent, an orphan medicinal product in "the treatment of Huntington's Disease", is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time.

The major objections precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies:

1. Efficacy was not proven in any of three pivotal trails
2. Major problems were found in the Pharmacokinetic part of the dossier

Deficiencies arising from concerns over the confidential (ASM - Active Substance Manufacturer restricted) part of the DMF are mentioned in the appendix (this appendix is not supplied to the MAA). These concerns will be conveyed in confidence to the holder of the DMF.

Questions to be posed to additional experts
N/A

Inspection issues
N/A

II. EXECUTIVE SUMMARY

II.1 Problem statement

Huntington's disease (HD) is an autosomal dominant, inherited, progressive degenerative neuropsychiatric disorder characterized by the development of emotional, behavioural, and psychiatric abnormalities, loss of previously acquired intellectual or cognitive functioning and movement abnormalities (motor disturbances).

HD is due to a mutation in a gene on chromosome 4 that is transmitted as an autosomal dominant trait. Mutations of the IT15 gene result in abnormally long repeats of DNA instructions. These instructions include unusual, repeated sequences of certain basic chemicals known as cytosine, adenine, and guanine or CAG trinucleotide repeats. These expanded CAG sequences result in the production of an abnormal protein named huntingtin.

HD is associated with progressive degeneration of neurons in certain regions of the brain and the presence of astrocytes that accumulate due to destruction of nearby neurons (gliosis). These neurodegenerative changes primarily occur within the caudate nuclei and the putamen, substructures of the basal ganglia that are collectively known as the striatum.

The symptoms of HD may vary in range and severity, age at onset, and rate of clinical progression from patient to patient–including among members of the same family (kindred). The peak age of adult-onset HD is between 35 to 50 years.

HD is classically associated with progressive emotional, cognitive, and motor disturbances. Early motor signs of HD typically include the gradual onset of clumsiness, balance difficulties, and brief, random, "fidgeting" movements. At first, chorea or frequent, irregular, purposeless, jerky motions, may be incorporated into intentional actions, potentially masking symptoms and delaying recognition of the condition. Early during the course of HD, chorea may be limited to the fingers or toes. However, these movements become more noticeable over time and may extend to the arms, legs, face, and trunk. Under certain circumstances, such as stress or a highly emotional state, choreic movements may become more pronounced. As the disease advances, chorea tends to become widespread or generalized.

There are no treatments available that alter the progression of HD and the treatment is currently based on a number of symptomatic drugs which are used for the control of chorea, rigidity, spasticity, and

dystonia. However, these drugs tend to provoke many adverse effects that limit their use and affect patient's compliance.

The present overview evaluates the clinical development programme of Ethyl-EPA 500 mg soft gelatine capsules in what is relevant to prove its safety and efficacy for Huntington's disease. Clinical trials and other research studies conducted in clinical situations other than HD will only be considered as supportive data when relevant.

II.2 About the product

Ethyl eicosapentaenoate (ethyl-EPA) is a substance with its safety profile already established prior to the start of its development for the treatment of Huntington's disease. The active substance is the ethyl ester of (5Z, 8Z, 11Z, 14Z, 17Z)-5,8,11,14,17-icosapentaenoic acid, a 20 carbon fatty acid with five cis-unsaturated double bonds. Ethyl-EPA acts as a pro-drug for EPA. EPA is a normal intermediate in animal and human metabolism, and is naturally obtained from the diet in the form of triglycerides. Ethyl-EPA is not a natural substance found in the diet, but it is hydrolysed in the intestine in a similar manner to triglycerides.

The rationale for the current clinical development is based on the fact that EPA, a member of the family of essential fatty acids, which are key membrane components, might compensate for membrane damage resulting from huntingtin accumulation. Ethyl-EPA, has been shown to affect mitochondrial function [Froyland 1997] by acting on peroxisome proliferator activator receptors (PPARs) [Jump 2002], preventing loss of neuronal function, inhibiting caspase activation and apoptosis, and reducing mitochondrial damage in models of neurodegeneration by reducing the activity of the JNK pathway [Puri 2005]. Thus, if ethyl-EPA were to have the capability of improving mitochondrial function in "suffering neurones" and to slow apoptosis, this might lead to an eventual slowing of neurodegeneration in the longer term.

II.3 The development programme/Compliance with CHMP Guidance/Scientific Advice

Ethyl-EPA has been licensed in Japan (Epadel®, 2700 mg/day) for the treatment of peripheral vascular disease and hyperlipidaemia. In the EU, ethyl-EPA is a component of a product used in secondary prevention after myocardial infarction and in endogenous hypertriglyceridaemia as a supplement to diet when dietary measures alone are insufficient to produce an adequate response (Omacor providing a combination of ethyl-EPA plus DHA, i.e. 1640 mg ethyl-EPA and 1440 mg DHA per day).

The Applicant presents studies with a soft-capsule formulation of ethyl-EPA on the pharmacokinetics (PK) in healthy subjects and patients and clinical efficacy and safety in patients with HD. Studies have previously been undertaken in other indications, including depression and schizophrenia, and data from these have been included in the safety database. Supporting information on human safety and PK of ethyl-EPA and EPA has also been drawn from published literature.

An unsuccessful MAA was submitted to the EMEA for Ethyl-EPA 500 mg Soft Gelatin Capsules, through the Centralised Procedure in 2003, using the proposed brand name LYXIA. The Pivotal Study LA 01.01.0005 of this application was a multicentre, randomised, double-blind, placebo-controlled, parallel-group, Phase II clinical trial comparing ethyl-EPA 2g/day to liquid paraffin placebo. It was undertaken in 135 patients with symptomatic HD confirmed by genetic tests or by positive family history. The Authority's Opinions questioned the conclusion of dose-proportionality of ethyl-EPA in the 1-2 g/day range and requested the Applicant to address possible interactions by identifying drugs that could potentially affect or be affected by ethyl-EPA administration. Discussion or studies for interactions with anti-aggregant and anticoagulant products were also requested.

The Applicant (Laxdale Ltd.) was subsequently acquired by the current Applicant, Amarin Neuroscience Limited, and has since performed and completed additional non-clinical and clinical studies which are included in this application.

II.4 General comments on compliance with GMP, GLP, GCP

GMP:
The CHMP has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

GLP
The GLP status of certain studies carried out in Japan and used in support of an application for marketing authorization in Japan is unknown.
The GLP status of published studies is unknown, including those that were published by the applicant.
The applicant should clarify the GLP status of all the studies which were carried out on his behalf (Laxdale Ltd or Amarin Neuroscience Ltd).

GCP:
The clinical studies are stated to be conducted in compliance with the requirements of Good Clinical Practice and the agreed ethical principles.

II.5 Type of application and other comments on the submitted dossier

This MAA is submitted as a full 'mixed' application in accordance with Article 8 (3) and Annex I part II.7 of Directive 2001/83/EC, as amended. The Applicant has included full chemistry, manufacturing and controls information, but the non-clinical and clinical information is based on a combination of studies sponsored by the Applicant and bibliographic references. The MAA is submitted via the Centralised Procedure under the mandatory scope of Article 3(1) Annex (4), orphan designated medicinal product, of Regulation (EC) No 726/2004.

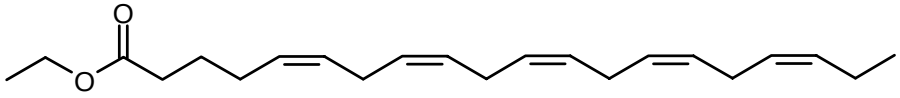
Ethyl Eicosapent 500 mg Soft Gelatin Capsules was designated as an Orphan Medicinal Product on 29/12/2000 and therefore falls under the scope of the Annex of Regulation (EC) No 726/2004. Ethyl Eicosapent 500 mg Soft Gelatin Capsules is eligible for evaluation under the Centralised Procedure under Article 3(1) of Regulation 726/2004 "Mandatory Scope". The sponsor report on the maintenance of the designation criteria was submitted to the EMEA 23/02/2009.

Ethyl-EPA capsules are previously known as Lyxia, Miraxion and LAX-101. Recently, the outcome of the CHMP's Name Review Group (NRG) discussion regarding the invented names proposed for this medicinal product (Dalsuva and Ozabla) was issued and is currently being reviewed by the applicant. Therefore, the applicant still wishes to use the INN, Ethyl Eicosapent as the product name for this marketing application, until a final decision regarding the invented names proposed is made.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance
Ethyl eicosapent soft gelatine capsules is a medicinal product for oral administration containing 500 mg Ethyl Eicosapentaenoate (Ethyl-EPA). The INN name is Ethyl Icosapent



The applicant has provided information relating to the manufacture, packaging, labelling, testing of Ethyl Eicosapentaenoate according to the ASMF procedure. The manufacturing process has been described - and substance-related impurities have been characterised.

Specifications and validated release tests are provided for assay, related substances and tests characteristics of polyunsaturated ester (peroxide, acid and saponification values).

Stability data up to 36 months at 25°C/60%RH are available for three pilot batches of EPA-E manufactured by previous process. Three pilot batches of EPA-E manufactured by the current process

proposed in the ASMF were also placed on long term stability studies and data up to 60 months are provided. 18 month data are also provided for one production batches. A photostability study has also been performed on one pilot batch and one production batch. All the provided results (photostability, long term and accelerated) are within specifications. The stability data support a re-test period.

Drug Product

The drug product will be provided as soft gelatine capsules at the strength of 500 mg per capsule. The applicant has provided information on the development pharmaceutics to justify the proposed formulation of the drug product in terms of optimising the relevant pharmaceutical attributes of the drug product such as stability. Valid TSE certificates of suitability are provided for gelatine.

The manufacturing process has been described by the applicant including the relevant critical process parameters and control.

There are no novel excipients used in the drug product formulation. All the excipients are compendial which are controlled to the requirements of the current monographs. No excipients of human or animal origin except for gelatine are used. Valid TSE certificates of suitability are provided for gelatine.

The applicant has provided specifications to control the quality of the drug product at release and at the end of shelf-life using an array of physico-chemical testing methods. Most of these tests are based on Pharmacopoeial methods. The other tests are adequately validated.

Long term and accelerated stability studies on pilot batches of drug product packed in PVC/PCTFE are available for three pilot batches and support the requested shelf-life for the drug product.

In conclusion, both the drug substance and the drug product have been sufficiently studied to ensure compliance with the relevant guidelines and batch to batch consistency. However, a few minor points as per the list of questions have to be addressed before marketing authorisation is granted to this product.

III.1 Non clinical aspects

This centralised procedure concerns Ethyl Eicosapent 500mg soft gelatine capsules. This product's active substance is ethyl eicosapentaenoate. It is indicated for the long term stabilisation of symptoms in Huntington's disease. The posology is a daily dose of 2 g ethyl eicosapent.

Ethyl eicosapentaenoate (ethyl-EPA) is a substance with its safety profile already established prior to the start of its development for the treatment of Huntington's disease. EPA has been used in EU (Omacor - EPA + DHA) as an adjuvant treatment in secondary prevention after myocardial infarction and in endogenous hypertriglyceridaemia, but not as a reference product in its own right. Moreover dietary supplements containing the free fatty acid form, eicosapent acid (EPA) have been available on a direct to consumer basis in the EU and USA for well over 10 years.

An application for a marketing authorization for this medicinal product was originally submitted to the EMEA on June 10th 2003 by Laxdale Ltd (now Amarin Neuroscience Ltd), under procedure No. EMEA H/C/553, but was subsequently withdrawn in February 2005. In the D180 joint Rapporteur's assessment report (JRAR), there were remaining clinical outstanding major objections. In the revised Non-clinical summary and non-clinical overview, the applicant did not consider the questions that were raised during the previous procedure in 2003-2004. On several issues the same questions rise and these have not been addressed by the applicant. The quality of the non-clinical dossier is considered poor. The applicant should have included the previous discussions in the new non-clinical dossier.

Published information has been used to support this application. Specific non clinical studies have been carried out on behalf of Laxdale Ltd in areas where insufficient information was available in the published literature. Some studies carried out in Japan were relied upon by the applicant.

In addition, the applicant has initiated a new non clinical development program for ethyl-EPA in support of its continuing development programme.

This application by Amarin Neuroscience limited is submitted under article 8(3) of Directive 2001/83/EC New active substance. The Applicant is requested to comment and justify why he feels that the use of bibliographic data can apply to the current application.

The GLP status of certain studies carried out in Japan and referred to in support of the application is unknown. The GLP status of published studies is unknown, including those that were published by the applicant. The applicant should clarify the GLP status of all the studies which were carried out on his behalf (Laxdale Ltd or Amarin Neuroscience Ltd).

Pharmacology

In general, the pharmacology studies are only weakly supportive of this application. In all the models tested, only two are directly relevant to the current application, *i.e*. to Huntington's disease: the R6/1 mouse and the YAC128 mouse. A moderate protection could be seen in a study with R6/1 mice, a transgenic HD model expressing the *exon* 1 of the human *HD* gene with 115 CAG repeats. However, this was obtained with a mixture of fatty acids containing only 3% EPA (and no ethyl-EPA). Only one study is directly relevant to this application. The study in YAC128 mice (transgenic mice expressing the human huntingtin protein with a 128 CAG repeat expansion) has shown a modest improvement of the motor function of treated mice. However, the treatment did not improve any aspect of striatal neuropathology. The panel of tests realized in both studies is limited. Effects of ethyl-EPA was not assessed in other HD models.

Other models were used by the applicant to try and demonstrate an effect of ethyl-EPA: models of dementia (aged rat and irradiated young rat) and a model of anxiety and depression (rat treated intracerebroventricularly with IL-1β). Both models arbour symptoms which are also exhibited by HD patients. However, this is hardly an acceptable justification since there exist multiple models of HD. Moreover the tests assessing learning, memory and anxiety used in these models of dementia, anxiety and depression could have been used in HD mouse models

In the models of dementia ethyl-EPA treatment resulted in an amelioration of long-term potentiation (LTP), a cellular mechanism underlying learning and memory. The mechanism of this protection is not Known. In vitro results suggest that it could be through the modulation of anti-inflammatory and pro-inflammatory mediators (IL-4, IL-1β), and of cellular pathways involved in apoptotic events. However, results of these experiments are not very convincing. For the aged rat model, statistics have always been done comparing treated aged rats to young rats stating that after treatment, there was not anymore a statistically significant difference between the two groups. No statistics were ever performed comparing treated aged rats and non-treated aged rats. Since effects observed are most of the time moderate it is doubtful there would be a difference.

In the Gamma-irradiated rat, which is rather a general animal model for the study of neurodegeneration, oral administration of presumably 5 mg/day ethyl-EPA for 4 weeks reversed the effects on LTP and apoptotic effects. It should be noted that dosing with ethyl-EPA in this study is inconsistently reported between Modules 2.4, 2.6 of the application and the original publication, which impedes the assessment. The applicant is therefore asked to clarify, which doses were indeed administered including also a potential dose-response relationship.

In the model of anxiety and depression (rats treated intracerebroventricularly with IL-1β) ethyl-EPA treatment was assessed in the Morris water maze, in the Elevated plus maze, a statistically significant improvement of the behaviour of the animals. In two studies two different doses of ethyl-EPA were assessed: 0.2 and 1%. A dose-related effect could be seen on most of the parameters assessed. However, the relevance of this model to the current application is questionable.

From a non-clinical point of view, the studies presented here are not clearly and specifically supporting the current application for the treatment of Huntington's disease. The proof of efficacy must thus rely only on clinical information. However, since the clinical efficacy has still not been clearly demonstrated, this constitutes a major clinical concern. In addition, it remains valuable to demonstrate the proof of concept in an appropriate animal model of disease. The applicant is requested to address this issue.

Concerning secondary and safety pharmacology the applicant reports different effects of EPA : serum lipid lowering effect, inhibition of platelet aggregation and thrombus formation and effects on the immune system.

The applicant states that interference with the coagulation pathway is only theoretical. However, in a publication from Mochida Pharmaceuticals (Saito 1989) it is said that ethyl-EPA has been developed

"as a therapeutic agent for chronic thrombosis and hyperlipidemia".Moreover, in rats and rabbits adverse effects on platelet aggregation were obtained at doses relevant to clinics (no safety margin). A warning that omega-3 acids demonstrated prolongation of bleeding time has been included in section 4.4. A warning for concomitant use of ethyl-EPA with anticoagulants has been included, but a warning for concomittant use of ethyl-EPA with antiplatelet agents is lacking. However, in clinical studies, no haemorrhagic events were seen in patients taking platelet aggregation inhibitors. Nevertheless, an active follow-up on spontaneous reports of haemorrhagic adverse events should be performed to confirm whether or not a drug interaction was involved. Use in haemorrhage should be contraindicated. In section 4.4, a statement to use with caution in patients susceptible to haemorrhage and in patients scheduled for surgery needs to be included.

The applicant did not discuss the immune effects of ethyl-EPA in its overview. However, results from the pre-clinical studies show that disease resistance is decreased by ethyl-EPA. In another study, Fritsche et al have demonstrated that dietary fish oil (esters of EPA and DHA) reduces survival and impairs bacterial clearance in C3H/Hen mice challenged by *Listeria monocytogenes* (Clin. Sci. 1997; 92:95-101). In the depression and anxiety model described above, ethyl-EPA exhibited anti-inflammatory properties. In the previous assessment procedure in 2004, the applicant was requested to integrate all the available information of the impact of Ethyl-EPA on the immunological system, namely derived from repeated dose studies and make a deeper analysis of the effects expected for Ethyl-EPA on immunity. The guidance given in the CPMP/SWP Repeated dose toxicity guideline and ICHS8 should be taken into consideration in this discussion. A discussion on the safety of EPA supplementation in immunocompromised patients should be performed. The applicant should include this discussion in the new non-clinical dossier. The applicant is also requested to include the observed non-clinical data with respect to the impact of Ethyl-EPA on the immunological system in section 5.3 of the SmPC.

The applicant has not conducted safety pharmacology studies to assess the potential for QT prolongation according to the recommendations provided in ICH S7B (Non-clinical evaluation of the potential for delayed ventricular repolarisation (QT interval prolongation) by human pharmaceuticals). Instead, the Applicant refers to the human pharmacokinetic study of ethyl-EPA in healthy subjects (LA 01.01.009) in which no evidence for drug-related QT/QTc interval prolongation is found. Postmarketing data for Epadel (300 mg ethyl-EPA) licensed in Japan since 1991 and Omacor (ethyl esters of EPA and DHA) have not demonstrated adverse events related to QT interval prolongation.

In a canine model of acute atrial tachypacing adult dogs received ω-3 fatty acids (including EPA) at a dose of 2.82 g/day (IV infusion over 65 minutes) and no change in P wave duration or in the PQ, QRS, QT or QTc intervals in any of the treatment groups was observed (data not shown in the publication). The treatment significantly reduced the shortening of atrial ERP, compared to both control groups. The same EPA+DHA infusion was given to dogs remaining in normal sinus rhythm. During sinus rhythm, EPA+DHA infusion did not alter any electrocardiogram (ECG) parameter or the atrial ERP (data not shown in the publication).

Taking into account that the non-clinical evaluation of the potential for QT prolongation seems to be supported by the in vivo study in the canine model of acute atrial tachypacing and by the provided clinical data (PK study and postmarketing data) further in vivo studies as recommended by ICH S7B are not required. However, ICH S7B also recommends the performance of an in vitro IKr study. The Applicant should explain why such a study was not performed.

Pharmacokinetics

Pharmacokinetic studies were previously conducted in Wistar rats and Beagle dogs to support an application for marketing authorisation of ethyl-EPA in Japan for the treatment of peripheral vascular disease.

In the current pharmacokinetic studies, the drug substance was administered by oral gavage, and was at least 90.5% pure. The same substance was used in the toxicology studies and the secondary pharmacology studies. The drug substance used in the pharmacology studies was approximately 95% pure. Relevance of these variations of purity to clinical lots is unknown.

Absorption

After oral administration of ^{14}C-ethyl-EPA, radioactivity was absorbed rapidly by the small intestine and transferred to the physiological circulation via the lymphatic system. The speed and degree of absorption were promoted by bile. Plasma concentrations reached peak value 6-9 hours (rats) or 24h (dogs) after administration, and then decreased in a biphasic manner. When administered daily for 12 days to rats, the blood and plasma concentrations at 24 hours reached steady state after 7 administrations. Rat kinetics are not linear, however, it may be acceptable that the nonlinearity is related with absorption, since the range of doses is very wide (30 to 1000mg/kg). Further non-clinical evaluation is not needed and this issue is to be handled clinically.

By nine hours after oral administration to rats, most of the radioactivity was detected in chylomicron and VLDL fractions in lymph and plasma. The radioactivity initially detected in the triglycerides decreased with time as that in cholesterol ester and phosphatidyl ethanolamine increased. Distribution of radioactivity in the liver, heart and brain showed a tendency to concentrate in phosphatidyl ethanolamine and phosphatidyl choline fractions. In the adipose tissue, most of the radioactivity was detected in triglycerides. No unchanged ethyl-EPA was detected in lymph, plasma, brain, heart, liver, adipose tissue, arteries or platelets. In dogs, most of the radioactivity was in LDL and HDL. Most of the radioactivity in plasma was bound to plasma protein in both rat and dog.

Distribution
In male rats (with the exception of the brain, white fat, skin and arteries, where the peak value was reached after 1 week), tissue radioactivity concentrations reached peak values after 9-24 hours then declined slowly. The elimination rate of radioactivity from the various tissues was the same as, or slightly lower than that from plasma. In female rats, concentrations in the brain, muscle, white fat and skin reached peak values after 1 week. The heart, adrenal gland, urinary bladder, ovaries, brown fat and bone marrow did so after 24 hours, the uterus after 9-24 hours and arteries after 24 hours-1 week. The peak values for all other tissues were after 9 hours. After repeat administration, the plasma concentration 24 hours after each daily administration reached a steady state after 12 days, but the concentration in tissues rose after each successive administration. No marked difference was noted between the elimination half-life of the various tissues after single administration and that after repeated administrations. The distribution of EPA within the body following administration of ethyl-EPA is similar to that following the administration of either the free acid or the triglyceride forms of EPA.

Ethyl-EPA showed considerably different distribution patterns among the species tested. In dogs, most of the compound was detected in LDL and HDL, whereas VLDL and chylomicrons were prominent fractions in rats. This was explained by divergent gastrointestinal absorption rates, which are slower in dogs compared to rats, although interspecies varieties in general lipid metabolism might have also played a role.

Metabolism
After oral administration of ^{14}C-ethyl-EPA to rats, EPA, DPA and DHA were identified in the liver as metabolites of ethyl-EPA. These metabolites were incorporated mainly into phospholipids and triglycerides. In rats the concentrations of EPA in red blood cell phospholipids, plasma phospholipids, plasma triglycerides, plasma cholesterol esters, liver phospholipids, liver free fatty acids, liver triglycerides and liver cholesterol esters increased in direct response to increasing levels of ethyl-EPA administered. Metabolism of ethyl-EPA is typical of fatty acids.

In summary, ethyl-EPA is acted upon by esterases in the small intestine to release free EPA, which is then incorporated into triglycerides, cholesterol esters and phospholipids. Thus, ethyl-EPA acts as a pro-drug for EPA.

Excretion
In rats, the excretion rates over 7 days in urine, faeces and expired air were 2.7%, 16.7% and 44.4% respectively in male rats, and 3.3%, 18.3% and 51.4% respectively in female rats. The biliary excretion rate up to 24 hours in rats was 2.9%. In dogs, the excretion was 1.0% in urine and 19.2% in faeces. When 14C-ethyl-EPA was administered orally to pregnant rats on the 12th and 19th days of gestation, a low rate of transfer of radioactivity to the foetuses was observed. The concentration in milk was higher than the plasma value 12 hours after administration and reached its peak value 24 hours after administration. This accumulation in milk is very clear (ratio milk/plasma between 10 to 20 at 24h, value estimated from the published graphic). Warnings are included in section 4.6 Pregnancy

and lactation but should be reworded according to the Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling (EMEA/CHMP/203927/2005). Excretion of ethyl-EPA is typical of fatty acids (SmPC Comment).

Pharmacokinetic drug interactions
Interactions of ethyl-EPA treatment with ticlopidine which exhibits inhibitory effect on platelet aggregation has been assessed in rats. No synergistic effect on bleeding time or ADP-induced platelet aggregation was observed when the two drugs were administered concomitantly, and only a slight effect on collagen-induced platelet aggregation was suggested.

No pre-clinical studies of co-administration with aspirin have been performed but clinical data is available: Mueller et al reported in 1991 that concomitant administration of a single dose of aspirin and omega-3 fatty acids (8g per day, including 3.5g EPA) did not prolong bleeding time. However, in the publication it is well stated that bleeding time is not prolonged as compared to olive oil. When compared to baseline values it seems well prolonged.

Doses of marine oil in excess of 3 g daily have been linked with an increase in bleeding time which were not associated with clinically significant bleeding. The haemorrhagic risk is mentioned in the SPC. As stated above, the warnings included are not considered sufficient. Use in haemorrhage should be contraindicated. In section 4.4, a statement to use with caution in patients susceptible to haemorrhage and in patients scheduled for surgery needs to be included (SmPC Comment).

Diet differences lead to different levels of omega-3 fatty acids assimilation in the population. In Mueller et al 1991, it can be read that "Greenlandic Eskimos, whose diets are rich in omega-3 fatty acids have significantly lengthened bleeding times compared with Danish control subjects" (Dyeberg J, Lancet 1979).

Altogether, all pharmacokinetic investigations were conducted in male animals apart from one study in rats. For this reason, the applicant should clarify potential differences between sexes with respect to available information from clinical use.

Toxicology
Most of the toxicity studies are provided in the form of published reports. These toxicity studies (except for the genotoxicity studies) were carried out in Japan for the purpose of a marketing authorisation application in Japan. No individual data were included and the GLP compliance is declared as unknown. This is considered not acceptable for an application submitted under the article 8(3) (directive 2001/83/EC) New Active Substance. The Applicant is requested to comment and justify why he feels that the use of bibliographic data can apply to the current application.

From the single-dose toxicity studies, it can be concluded that the acute toxicity of ethyl-EPA and metabolites and impurities tested is low. Metabolites of ethyl-EPA were also administered in the single-dose study, and the mortality rate of rats treated p.o. with 20g/kg EPA or DHA was of 9/10 and 8/10, respectively.

A repeat-dose toxicity study in non-rodents is lacking.

In rats, the findings observed after 3 and 12 months administration of ethyl-EPA were similar. In both studies, the estimated no effect dose of ethyl-EPA was 0.1g/kg/day.

In the 12 month repeat-dose toxicity study there were four fatalities (one male in the 3g/kg group and one female in each of the control, 1 and 3g/kg groups). It was thought that the deaths were caused by accidental overdose of Ethyl-EPA.

No toxicokinetics were performed in the two rat studies. No final conclusions can be drawn with respect to the safety margin to the clinical exposure. However, from extrapolation of the kinetics from the pharmacokinetic studies to the toxicology study, an assessment of safety margins for the effects seen in toxicity studies is possible, although this is far from ideal. It seems that at the NOEL of 0.1 g/kg, the exposure would be similar to the exposure in humans treated with a 2g dose. The pharmacological effects (decrease of blood lipids) occur in the same range of exposure. Other effects were observed at higher doses, with a possible safety margin to be defined.

Five genotoxicity studies were performed, including one in vivo study (mouse micronuclei in bone marrow). The reverse mutation assay and the in vivo study gave negative results. However, the three chromosomal abberations studies in mammalian cells were positive.

The genotoxicity observed in vitro could be due to the impurities present in the product at relatively high concentrations in the pre-clinical batches (10% for the toxicology studies). However, the specifications for ethyl-EPA and batch analysis results indicate that the impurities observed are related substances derived from raw materials or from isomerisation of the active substance. None of these substances require qualification.

Since the clastogenic effects of ethyl-EPA and EPA were observed at concentrations that were reported to produce significant cytotoxicity and since the results of the in vivo experiment is negative, it is not considered that further studies are requested to clarify the genotoxic potential of ethyl-EPA.

In the in vivo study, the dose of ethyl-EPA administered is defined as ml/kg. This does not allow comparison of doses with other studies. The applicant should provide doses in g/kg.

A 2-year carcinogenicity study of ethyl-EPA was conducted in male and female Wistar rats (Report IR 23040). Doses evaluated were 0.1, 0.3, and 1.0 ml/kg/day.

There was an increase in the incidence of fibrosarcoma (skin and subcutis) in males of the medium and high dose groups and in the incidence of anterior lobe pituitary adenoma as a cause of death in females at 1.0 ml/kg/day. Both increases were not statistically significant and not observed in the other gender group. However, the applicant is asked to assess the human relevance of the tumour findings observed in the carcinogenicity study in rats considering the PPAR agonistic activity of ethyl EPA.

For females, mortality was found to be statistically higher in the highest dose group (1.0 ml/kg/day) compared with Control 1 ($p<0.001$) and females from this group were sacrificed after 98 weeks of treatment. Other gender differences in this study include a significant reduction in food consumption and body weight, higher incidences of gastric ulceration and reduced platelet counts in females.

Since the dose of ethyl-EPA administered is defined as ml/kg, a comparison of doses with other studies is not possible. Moreover, pharmacokinetics at different doses are not available for female rats. The applicant should provide doses in g/kg and discuss the relevance of the gender specific differences observed in the carcinogenicity study.

In the rat fertility and early embryonic development study, ethyl-EPA administered at 0, 0.3, 1.0 or 3.0 g/kg/day showed no effects at any dose on copulation, fertility, viability or development of the foetuses, and no teratogenic effects. The applicant considers that the NOEL for effects on reproduction and on the next generation is 3.0 g/kg/day. However, a statistically significant increase in the incidence of cervical rib variations was observed in the 3.0g/kg group. This was considered not relevant by the applicant since the overall incidence of skeletal abnormalities is not increased. It should be concluded that ethyl-EPA did not induce significant effects on animal fertility and early embryo-foetal development up to the dose of 1g/kg.

In the rat embryo-foetal development study, isolated cases of absence of optic nerve were noticed: 1 case in each treated group, not in control group. According to the applicant, this is considered incidental since in the fertility study 3 cases were noted in the control group and none in the three treated groups. During the previous assessment procedure, the applicant was requested to provide historical data of the same strain of rats, bred at the same animal facility. The reported historical cases point towards a hazard distribution of the optic nerve abnormalities in foetuses. In one study 3 cases from treated group were seen, in another study three cases in controls. A concern does not seem plausible.

In the rabbit embryo-foetal development study, an increased number of resorbed and dead foetuses was noticed at the dose of 1g/kg. This increase was mainly ascribed to a single female which showed marked body weight loss and only resorbed foetuses.

In the rat prenatal and postnatal development study (including maternal function), a reduced fertility in male offspring (↓ copulation (3 g/kg) and fertility (0.3 g/kg) rates in males) is reported. However, considering the specific patient population the drug is intended for, this doesn't seem to represent a major safety concern. Nevertheless, this needs to be mentioned in the SmPC, sections 4.6 and 5.3 (SmPC Comments).

An environmental risk assessment (ERA) was provided by the applicant. This ERA is not in line with the Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labeling (EMEA/CHMP/203927/2005). However, ethyl eicosapent is the ester of eicosapentanaeoic acid, a naturally occurring fatty acid. Fatty acids and their esters are lipids (IUPAC) and as such are exempted. There is thus no need for further assessing a potential environmental risk.

III.2 Clinical aspects

Pharmacokinetics

Ethyl-eicosapent acts as a pro-drug for eicosapentaenoic acid (EPA), since no ethyl ester has been detected. EPA ethyl ester is poorly absorbed as compared with the triglyceride form from single doses with no food or low-fat food, but the absorption is significantly increased when co-ingested with fat (either as high-fat meal or as olive oil) from single doses, or with a regular meal from multiple doses as compared with the triglyceride form. Therefore EPA is incompletely absorbed from oral administration, but absorption is largely improved when co-administered with fat. Thus it is recommended that the drug is taken with or after food.

The applicant performed one classical PK study (study LA01.01.0009). Results show a rapid increase of EPA in plasma (Tmax of 4.64 h). The PK profile for EPA showed a low clearance with extensive distribution (Vss = approx. water body volume), typical of long chain polyunsaturated fatty acids. Volume of distribution at steady-state is reported as 62.8±25.7 L. Red blood cell accumulation is ca. 4 fold as compared to baseline after at least 1 month multiple dosing. This is an important finding provided it is predictive of prevention of damage to cell membranes as claimed. No protein binding studies have been performed. This should be done, due to the known role of plasma proteins in fatty acid transport

The elimination half-life is 42.2±30.9 hours and the clearance 1.3±0.8 L/h. The rate of incorporation of EPA in red blood cells (RBCs) was, however, slower than the increase in plasma EPA, with only a slight increase in RBC EPA levels being seen 48 hours post-administration. Red blood cell accumulation has been investigated.

From study LA01.01.0001 (schizophrenia efficacy/safety study) it is concluded that RBC EPA concentrations increase in function of the administered dose.

It is speculated that the normal metabolic pathway for endogenous polyunsaturated fatty acids (PUFA) is followed by EPA. EPA is beta-oxidised and further metabolised by the tricarboxylic acid cycle and finally excreted as carbon dioxide and water. According to the applicant EPA metabolisation involves only 2 metabolic routes : (i) the cyclooxygenase (COX) pathway producing prostaglandins and thromboxanes, and (ii) the lipoxygenase (LOX) leading to hydroxyl metabolites. However, there is a third major metabolic route, involving the cytochrome P450 (CYP) pathway implying oxidation by monooxygenases to produce hydroxylated and epoxidised fatty acids. This metabolic route has not been discussed by the applicant.

Plasma and RBC levels have been determined in study LA.01.01.0005 performed in 67 Huntington's disease patients and in study LA.01.01.0001 in 26 schizophrenic patients but the only data reported is the accumulation in RBC. No specific studies have been carried out by the Applicant to assess the effects of age, sex, race, weight, renal or hepatic impairment on PK. No specific drug interaction studies have performed.

In conclusion, several important parts to characterize the pharmacokinetic profile of EPA are missing:

- Although preclinical studies in rats and dogs indicated that a high degree of serum protein binding exists for this compound, protein binding in humans has not been studied. This should be done, due to the known role of plasma proteins in fatty acid transport.
- The excretion has not been formally studied and published data is scarce. The applicant should discuss the excretion pathway (after metabolisation of EPA) more into detail and to show data on % renal, hepatic and pulmonary excretion.
- One of the most important parts missing in the file is the discussion of the CYP metabolisation of EPA. Indeed, numerous publications show that CYP2C9/2C19 and 1A2 were the most efficient in EPA and DHA epoxidations and that EPA is not only a substrate for these enzymes, but also a

potent inhibitor of CYP2C9 and CYP2C19. In addition, it appears that also some members of the CYP4F subfamily are involved in the metabolism of EPA. Moreover, CYP2C9, 2C19 and 1A2 are subjected to genetic polymorphism and the degree of genetic polymorphism is dependant of the race.

- Dose-proportionality has not been appropriately demonstrated as the data shown concern only the incorporation in RBCs. No data in plasma have been presented.
- Likewise, no data on the intra-individual variability have been presented.
- Although it is clear from the available information that an altered pharmacokinetic profile of EPA in patients with impaired renal and/or hepatic function could exist, the applicant has not performed a single experiment in these special populations.
- The applicant claims that published clinical data supports the safety of ethyl-EPA with a wide variety of concomitant drugs. However, from the available literature it is clear that different interactions with EPA could occur (interactions with CYP substrates, interactions with lipophilic substances and interactions with other fatty acids in the cells). These have been by far not explored by the applicant. As this can have a major impact on the efficacy and safety profile of this medicinal product, all of the aspects described above should be taken into account and appropriately addressed by the applicant.

Therefore, it can be concluded that the same conclusions as those made during the unsuccessful MA in 2003 apply. No new PK studies have been included in the application file. The substance is not sufficiently characterised in terms of its pharmacokinetics and a favourable opinion on this section of the file cannot be granted.

Pharmacodynamics

The documentation on clinical pharmacodynamics is poor and indirect. The mechanism of action is unknown and it is only suggested that increased EPA concentrations in cell membranes may prevent their damage. The red cell fatty acid concentration is considered a good surrogate of neural membrane fatty acid content. However, this assumption is only based on an old study in rats (1987), which demonstrated that red blood cells and neural membranes showed the same relative effects of modification of dietary lipids on the composition of very long chain poly-unsaturated fatty acids. High and low CAG groups had the same raise in EPA red blood cell levels. Patients in the high CAG group showed a greater fall in AA that those in the low CAG group. This difference, which was not statistically significant, may provide some further evidence for the biological difference between patients with high vs low CAG repeat numbers, but can hardly explain the alleged different clinical response to EPA in the two groups.

So in general, the pharmacodynamic characterisation of ethyl-EPA is rather deficient and this undermines the case of the applicant because there is no solid biological rational for the therapeutic claim.

Clinical efficacy

Dose-response studies and main clinical studies

There were no formal dose finding studies done. The dosage used in the pivotal trials was based on the findings in a pilot study involving seven HD patients. Neither were formal dose response studies undertaken, but data was gleamed from a study in schizophrenia patients treated with a range of ethyl-EPA doses. As a result, treatment consisted of ethyl-EPA in a 2g/day dosage schedule. Furthermore, the applicant argues that doses of EPA below 3 g per day are not expected to be associated with an increase in bleeding time.

The applicant submitted three pivotal trial reports in support of their application. These entailed one phase II and two phase III studies. These three trials had an overall similar design philosophy, with a double blind, randomised, parallel group and placebo controlled phase followed by an open-label phase in which all participants, regardless of the treatment undergone in the randomized phase, received the study product. The main difference between the three trials pertained to the phase durations. Study LA001.001.0005 had two phases of 12 months each, while the two phase III trials (AN01.01.0011 and AN01.01.0012) were planned to have phases of 6 months. In case of study AN01.01.0012, the open label phase was only added after a protocol amendment.

Study ID	Trial Design	Ethyl-EPA dose/day	Duration	Diagnosis Incl. criteria	Total number of patients db: randomized (completed) [ole: enrolled (completed)]
Study LA01.01.0005	mc, random, db, pc	2 g ethyl-EPA/day administered as two 500 mg capsules b.i.d.	12-months db, (12 months ole)	HD stage I or II	db: 135 (121) [ole: 120 (110)]
Study AN01.01.0011			6-months db, (6 months ole)	ambulatory HD patients, not requiring skilled nursing care	db: 316 (301) [ole: 296 (193)]*
Study AN01.01.0012					db: 290 (273) [ole: 236 (1)]*

mc= multicenter, random= randomized, db=double blind, pc=placebo controlled,
ole= open label extension period
* = open label extension period was terminated early after the results of the db phase of study AN01.01.0011 revealed no benefit

The primary objectives for all three studies was to examine the effect of ethyl-EPA versus placebo on the motor phenotype of HD patients as measured by the Total Motor Score-4, derived from the Unified Huntington's Disease Rating Scale Total-Motor-Score subscale by omitting hard to score or high cognitive aspect containing items, during the randomized and during the open-label phase.

Secondary objectives were to examine the effect of ethyl-EPA versus placebo on the Total Motor Score component of the UHDRS; maximal chorea as measured by the UHDRS-Motor subscale; color naming as measured by the UHDRS Cognitive subscale; symbol digit as measured by the UHDRS Cognitive subscale; Clinical Global Impression (CGI) score judged by the Investigator, TMS-4 responder rate as measured by the UHDRS; bradykinesia as measured by the UHDRS; dystonia as measured by the UHDRS; Independence as measured by the UHDRS; functional scores (finances, domestic chores, activities of daily living [ADL] responders) as measured by the UHDRS, patient improvement assessment as measured by the UHDRS; the Mini-Mental State Examination (MMSE); the Beck Depression Inventory-II (BDI-II) and finally the analyses of the red cell membrane fatty acid levels (essential fatty acids).

The pre-specified primary endpoints were thus the Total Motor Score-4 (TMS-4) subscale of the UHDRS at 12 or 6 months (studies LA01.01.0005 and AN01.01.011/012 respectively). All other UHDRS, total UHDRS and USRSDS scores were considered secondary variables. In AN01.01.011 and its European parallel study CGI global improvement was also assessed at 6 months.

All three studies failed to attain the primary endpoint. In study *LA01.01.0005*, the effects of ethyl-EPA and placebo could not be distinguished in the protocol pre-specified ITT analysis. Differences were demonstrable in the PP population and in the sub-population of patients with CAG ≤44. Analysis of the PP population (representing about 60% of the ITT population) showed a borderline significant difference between ethyl-EPA and placebo in TSM-4 (p=0.061) and a significant difference in TSM (p=0.046) in favour of ethyl-EPA. In the classification of 'Improvement/No Change' versus 'Deterioration' at Month 12 significantly more patients in the ethyl-EPA group judged to have shown 'Improvement/No Change' in TMS-4 (69%) compared to the placebo group (48%) (chi-square p-value=0.0477).

In the CAG ≤ 44 subgroup a significant difference in favour of ethyl-EPA was seen for TMS-4 in the ITT as well as in the PP population.

In the analysis of patients treated for at least 12 months, patients originally randomised to placebo and subsequently switched to ethyl-EPA showed a response that was of a similar magnitude to that shown by patients treated with ethyl-EPA.

In study *AN01.01.0011*, the randomised phase of the study analyses of efficacy variables showed no notable or statistically significant difference in favour of ethyl EPA. Analyses of the open-label data for patients treated up to 12-months showed a significant treatment effects with ethyl-EPA in the ITT population (with respect to TMS-4, TMS and maximal chorea score). The results are not adjusted for multiplicity of testing and the findings might have been influenced by selection bias and bias due to knowledge of treatment during this study phase and therefore cannot be seen as conclusive.

Study *AN01.01.0012* demonstrated no differences between ethyl-EPA and placebo. A high placebo response was observed. The expected deterioration in motor function of HD patients given placebo only was not observed in this study. This finding does support the fact that the claimed long-term superiority of the ethyl-EPA treatment compared with placebo is not a consistent observation in all phase III studies.

In contrast, there were also a number of results found which seemed to favour placebo treatment.

In study **LA01.01.0005** the difference in the behavioural sub-score at months 12 approached significance in favour of placebo in the ITT population (p=0.093; the only result of the ITT analysis which approached statistical significance) as well as in the PP population (p=0.094) and reached statistical significance in the post-hoc subgroup analyses of ITT patients with CAG > 44 (p=0.05) and with baseline TSM-4 ≥ 26 (p=0.018), respectively.

In addition, the post-hoc subgroup analyses revealed the following striking results: In the ITT CAG > 44 subgroup there was a significant treatment difference in TMS-4 (p=0.022) as well as in TMS (p=0.042) in favour of placebo at month 6 (which were both no longer evident after month 12). However, for these comparisons the significance level was not adjusted for multiple testing.

Whereas in study **AN01.01.0011** TMS-4 score, TMS score and maximal chorea score showed a numerical advantage of ethyl-EPA after 6 months (in the mFAS ≤ 44 and the mFAS-all population), results for the cognitive scores tended to be in favour of placebo: The colour naming score showed a numerical advantage of placebo in the mFAS-all population and the symbol digit modalities score showed a numerical advantage of placebo in the mFAS ≤ 44 and the mFAS-all population.

During the double-blind study phase, the results of the CGI showed a numerical superiority in favour of the placebo group in all populations (FAS ≤ 44, FAS-all, PPS ≤ 44 and PPS-all, respectively).

The analyses of the additional efficacy parameters did not show any significant treatment differences, some of them were numerically in favour of placebo which is considered especially relevant concerning the parameter percentage of patients with at least 20% improvement from baseline to 6 months in TMS-4 , which was pre-specified in the protocol as a measure of response.

Concerning the double blind phase of study **AN01.01.0012** there was only one significant difference (at the non-adjusted 0.05 type I error level) between the treatment groups: Mean colour naming score was significantly greater (i.e. better; p=0.0178) in the placebo group than in the ethyl-EPA group for the FAS-all study population. Concerning the primary efficacy parameter (i.e. the mean change of TSM-4 at 6 months in the FAS ≤ 44 population) no difference was seen between the treatment groups. However, a numerical advantage of placebo was seen for the TSM-4 in the FAS-all population and for the TMS in the FAS ≤ 44 and FAS-all population. The only significant result reported for the open-label phase of study AN01.01.0012 was again in favour of placebo: The L.S. mean difference in change in maximal chorea score from 6 months to 12 months in the FAS-all population (p=0.028).

An ancillary analysis was done to look at the long term rate of deterioration of patients taking ethyl-EPA versus those taking placebo. Since there was no long-term data, it was generated using linear regression of placebo data from an unrelated study. This was considered appropriate by the applicant due to similarity of the demographic data between the two studies. This way, the applicant claimed there to be a significant difference in deterioration rate in favour of the ethyl-EPA group. However, this way of generating placebo data from a non-related study, solely based on the argument that the placebo groups between studies were of a similar profile, is highly questionable.

The suggestion arising from Study LA01.01.0005 that Ethyl-EPA Capsules might have been more effective in HD patients with ≤44 CAG repeats, a specific analysis of which was built into the Phase III study design, was not confirmed. On the basis of the analyses of the two Phase III studies, the applicant comes to the conclusion, that the treatment response of ethyl-EPA would more likely be influenced by treatment duration. However, in study LA01.01.0005 no significant results were seen in favour of ethyl-EPA in the ITT analyses after 12 months of double-blind treatment. Furthermore, in study AN01.01.0012 not even a slight trend in favour of ethyl-EPA could be constituted.

Moreover, the argumentation that improvement during the open-label phase of study LA01.01.0005 was irrespective of prior randomisation is not consistent with the finding of study AN01.01.0011 showing no statistically significant difference between ethyl-EPA and placebo during the double-blind phase but a significant difference after **both** treatment groups have been treated with ethyl-EPA for a further 6 months.

Summed up, based on the results of the three phase II and III studies efficacy of ethyl-EPA in the claimed indication, it is the CHMP's opinion that efficacy has not been adequately proven for this product in the indication: 'Long-term stabilisation of symptoms in patients with Huntington's disease'. Moreover, the presented negative results can not be compensated on the basis of the presented post-hoc analyses

Clinical studies in special populations
Not Applicable

Analysis performed across trials (pooled analyses AND meta-analysis)
Longitudinal analyses were performed for the randomized phase of studies LA 01.01.0005 (up to 12 months), AN 01.01.0011 (up to 6 months), AN 01.01.0012 (up to 6 months), as well as for the randomized plus open-label phases of study AN 01.01.0011 (up to 12 months). The results are summarized in the table below:

	ITT		ITT, CAG ≤44		PP		PP, CAG ≤44	
Study	Mean Difference	P-value*	Mean Difference	P-value*	Mean Difference	P-value*	Mean Difference	P-value*
LA 01.01.0005 (12 months)	-1.046	0.157	-2.707	**0.000**	-2.351	**0.027**	-4.882	**0.003**
AN 01.01.0011 (6 months)	-0.857	**0.047**	-0.498	0.202	-0.722	0.098	-0.581	0.185
AN 01.01.0011 (12 months) - Restricted[1]	-1.470	**0.010**	-1.015	0.088	-	-	-	-
AN 01.01.0011 (12 months) - Unrestricted	-1.186	**0.012**	-0.791	0.089	-	-	-	-
AN 01.01.0012 (6 months)	-0.095	0.441	-0.513	0.274	0.025	0.517	-0.355	0.354

*One-sided p-values are presented.
[1] Censored to those subjects with 12 month assessments completed before April 24, 2007, when the results of the double-blind phase of the study were made public.

The objective of these longitudinal analyses was to compare the differences in TMS-4 score change from baseline across all available points in time, rather than the difference in TMS-4 score change from baseline between ethyl-EPA and placebo at one specific time-point as in the protocol pre-specified analyses.

Using the change of the TMS-4 from baseline the data from all applicant sponsored studies at all time points was linearly combined to calculate an "observed Z-statistic" stratified for different factors to compare regional data or data by center. Non-parametric methods were used for the calculations to provide a robust estimation of the summarized effect. The inverse variance weighting method was used for inclusion of weights for the single data points. The permutation test method was used to obtain a level of significance when compared to a constructed reference distribution.

This multivariate method of analysis is not a standard statistical method and was specifically tailored for the results of the applicant sponsored data. The results were not consistent for the presented set of studies. Coupled with the fact that this is a post-hoc analysis, their value in supporting the applicant's claim is very limited.

The results are not consistent throughout the whole set of populations and studies, but show significant results for different subpopulations:

Supportive study(ies)
A number of patients in one of the study centres underwent MRI scanning of the brain during the randomized double-blind phase to assess the effects of ethyl-EPA at 0, 6 and 12 months. The table below gives the voxel-wise analysis of this data:

Time period (months)	Group	n	Mean change	S.E.	GLM	Permutation test
0 to 12	Ethyl-EPA	14	-0.75257	0.230026	p<0.067	p<0.068
	Placebo	16	-1.22381	0.201256		
0 to 6 (inclusive)	Ethyl-EPA	16	-0.3175	0.14457	p<0.05	p<0.048
	Placebo	18	-0.61511	0.080764		
7 to 12 (inclusive)	Ethyl-EPA	14	-0.53964	0.185158	NS	NS
	Placebo	16	-0.59875	0.162396		

Source: see Module 5, Study LA01.01.005 [Puri 2008].
NS: Not statistically significant (p>0.05)

Overall, the applicant concluded that patients treated with Ethyl-EPA capsules had a reduced mean rate of atrophy in all comparisons with the placebo group. A significant difference in global cerebral atrophy was found between the ethyl-EPA group and the placebo group during the first 6-months of treatment, while during the second 6-month period the rate of global atrophy was similar in both groups.

Significant group-level reductions in brain atrophy were observed in the head of the caudate nucleus and the posterior thalamus (voxel-wise analyses). The effect seen by month 6 had however ceased after 12 month. Thus, the time course of the differences of the MRI does not correlate with the time course of the treatment effect of ethyl-EPA postulated by the applicant. Furthermore, the time course of the differences in MRI does not correlate with the assumed time course of clinical efficacy of ethyl-EPA. These data cannot be considered confirmative for efficacy.

Clinical safety
The assessment of safety of Ethyl-EPA 500 mg Capsules is based on the safety data obtained during eight ICH-GCP clinical studies conducted by the Applicant, not only in HD but also in depression and schizophrenia. Seven of these were randomised, placebo-controlled clinical studies in patients (LA01.01.0001, LA01.01.0002, LA01.01.0005, LA01.01.0006, LA01.01.0008A, AN01.01.0011, AN01.01.0012), and one was a PK study in healthy volunteer subjects (LA01.01.0009).

Supportive safety information is provided from nine Investigator-led studies: LA01.02.0008, LA01.02.0015, LA01.02.0016, LA01.03.0001, LA01.03.0008, LA01.12.0001, LA01.13.0001, LA01.13.0002 and LA01.13.0003. The Investigator-led studies are reported as manuscripts in the scientific literature, but full formal analyses of the safety data are not generally available.

In total, 1149 patients or healthy volunteer subjects were enrolled in the eight ICH-GCP-standard clinical trials, receiving a daily dose of 0.5 to 4 g/day ethyl-EPA, with treatment periods lasting from 1 month up to 2 years.

The three applicant-sponsored efficacy studies in HD (LA01.01.005, AN01.01.0011 and AN01.01.0012) included 741 male and female patients of any race, though the majority of patients were Caucasians, aged 29-84 years inclusive, who had a confirmed diagnosis of HD (positive family history and/or genetic analysis). During the clinical programme, studies to support the efficacy of Ethyl-EPA Capsules were conducted in North America and Canada, Western Europe and Australia.

The Phase III Studies AN01.01.0011 and AN01.01.0012 in HD patients were designed based on the results of the LA01.01.0005 study. Patients were in HD Stage I or II, as assessed by dystonia/bradykinesia/chorea UHDRS scores. The main difference in study design was a modification of the inclusion criteria to select patients who were thought most likely to benefit from ethyl-EPA on the basis of the biological characteristics of the patients from Study LA01.01.0005. The Phase III programme therefore enrolled patient populations that included approximately two-thirds of patients with cytosine-adenine-guanine (CAG) repeats $\leq$ 44, with the aim of selecting mild to moderate

patients based on clinical criteria, rather than more severe patients or younger age of onset (which relates to larger CAG repeat length).This has to be reflected in the wording of the indication.

No important unwanted effects of ethyl-EPA have emerged from the clinical studies. Pooled results of the eight randomised clinical studies (including seven placebo-controlled studies) with Ethyl-EPA 500 mg Soft Gelatin Capsules showed that the incidences of AEs in the ethyl-EPA group were generally not different from the incidences of the same events experienced by patients on placebo. The adverse effects were mainly mild to moderate in intensity.

The most common AEs observed during the double-blind phase of the Applicant's studies were related to the gastrointestinal system with diarrhoea/loose stools being the most common AE reported in both ethyl-EPA and placebo groups. Episodes of diarrhoea were generally transient and self-limiting.

Diarrhoea was also commonly reported during the open-label phases, although in studies LA01.01.0005 and AN01.01.0011 the most frequently reported event was fall. This was not generally considered to be related to study medication as it was considered to be a consequence of HD.

The other most commonly reported (≥ 3 %) AEs in patients receiving ethyl-EPA treatment, across all phases of treatment included other gastrointestinal events, such as flatulence, nausea, and depression, insomnia, anxiety, irritability, fatigue, chorea and balance disorder. The majority were not considered related to ethyl-EPA.

Among the gastrointestinal AEs, diarrhoea occurred in slightly fewer patients on active [9.0%] than on placebo [11.1%; all double-blind studies]. This is not unexpected in that placebo was also an oily, liquid paraffin, which can be expected to have cumulative effects as a lubricant faecal softener on continued dosing. About 3.5% HD patients experienced nausea while taking ethyl-EPA compared with 2.4% on placebo [all double-blind studies]. There were no marked and clinically significant changes in the results of laboratory safety tests, vital signs or physical examination following treatment with ethyl-EPA.

With the possible exception of diarrhoea, the AE profile did not appear to be affected by duration of use and ethyl-EPA did not enhance the side-effects of any concomitant treatments taken by patients in these studies. A thorough sub-group analysis however was not provided.

There is a theoretical possibility that ethyl-EPA may increase the effect of anti-coagulant medication. One of the pharmacological actions of ethyl-EPA is the inhibition of platelet aggregation and the suppression of platelet adhesion in patients with thrombotic and arteriosclerotic disorders. This pharmacological action provides the basis for the marketed indication in Japan.

The interactions problem was insufficiently studied because no specific studies were conducted. However, a review of AE data of 44 subjects exposed to 4 g/day ethyl-EPA for up to 12 weeks in studies LA01.01.0001 and LA01.01.0002 revealed no apparent effect on bleeding time.

No such adverse events have been observed in clinical trials.

The applicant states that on one hand patients taking anticoagulants were excluded from HD studies and on the other hand patients on antithrombotics did enter the studies. This discrepancy should be clarified. In fact, there are a number of discrepancies on several topics and conflicting numbers reported in different sections of the dossier that should be clarified (see Section IV).

In face of the rational for interactions with antiaggregant products and with anti-coagulants formal studies should be done. The contraindications and warnings are appropriately addressed in the SPC. Section 4.8 needs revision.

Overall, the AE profile was acceptable for a long-term treatment of patients with early HD (mild to moderate disease), with no important events being attributable to the drug.

Pharmacovigilance system

The applicant has provided documents that set out a detailed description of the Amarin system of pharmacovigilance (Version 2.0 dated 02 April 2009). A statement signed by the applicant and the qualified person for pharmacovigilance, indicating that the applicant has the services of a qualified

person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided.

The CHMP considers that the Pharmacovigilance system as described by the applicant has to be completed in order to fulfil the requirements:

1. As neither the Qualified Person Responsible for Pharmacovigilance (QPPV) nor the QPPV deputy are medically qualified, the applicant should provide details about their access to a physician or a team of physicians.
2. The QPPV has to be registered to Eudravigilance system. A copy of this registration should be provided.
3. The description of the organisation should include links with other departments involved with pharmacovigilance activities (e.g. regulatory affairs, marketing, quality assurance) and a brief summary of pharmacovigilance activities undertaken by each unit. The flow chart illustrating the flow of safety reports should be expanded to provide timelines for the individual steps.
4. Those SOPs designated as in progress should be finalised as soon as possible and at the latest before the product is placed on the market. A SOP for the topic "meeting commitments to competent authorities in relation to a marketing authorisation" should be established before the marketing authorisation is granted to be able to deal with potential commitments conditional to the granting of the marketing authorisation.
5. A Pharmacovigilance service provider has been chosen by Amarin as the Pharmacovigilance service provider. The DDPS version 1.0 stipulates that a contract will be in place between Amarin and The service provider which specifies roles and responsibilities for all pharmacovigilance related activities, and outlines the responsibilities of both the QPPV and AMARIN in executing and supporting the QPPV role respectively. However, agreements with licensing partners have not been finalised. Those agreements should be finalised prior to marketing of Ethyl eicosapent soft gelatine capsules and the applicant is requested to provide this information in order to complete this DDPS.
6. The location of training records, CVs and job descriptions should be provided (especially for Amarin staff).
7. The characterisation of the quality management system should include more information on the aspect quality assurance (documentation of the internal audits of the pharmacovigilance system, responsibility for ensuring resulting corrective and preventive action).
8. The applicant is requested to submit a revised description of the pharmacovigilance system answering the above-mentioned questions.

Provided that the deficiencies are rectified prior to the applicant placing the medicinal product on the market, the CHMP may consider that the Pharmacovigilance system will fulfil the requirements. The applicant must ensure that the system of pharmacovigilance is in place and functioning before the product is placed on the market

Risk Management Plan

The Applicant submitted a risk management plan, which included a risk minimisation plan.

The CHMP, having considered the data submitted in the application, was of the opinion that the efficacy of the medicinal product had not been established based on the data submitted. In the absence of established efficacy, it cannot be assessed if the proposed risk minimisation activities would be adequate in reducing the risks to an acceptable level that will render the risk/benefit balance positive. Therefore, the CHMP was of the opinion that risk minimisation activities cannot be agreed at this stage.

IV. ORPHAN MEDICINAL PRODUCTS

According to the conclusion of the COMP (Opinion dated 29/12/2000) the prevalence of the "condition" Huntington's Disease is between 0.4 and 0.7 per 10000 (15000-26000 per 377000000) individuals in the EU.

Orphan drug status has been granted for ethyl-EPA in the treatment of HD and the medical need of effective treatment in patients with HD is undoubted. For ethyl-EPA the applicant claims a positive effect on the motor symptoms of HD but not on the behavioural or cognitive symptoms of HD.

V. BENEFIT RISK ASSESSMENT

V.1 Benefits

All three pivotal clinical studies submitted as supportive evidence for this application failed to attain their primary endpoint.

In study **LA01.01.0005**, the effects of ethyl-EPA and placebo could not be distinguished in the protocol pre-specified ITT analysis. Differences were however demonstrable in the PP population and based on a post-hoc analysis in the sub-population of patients with CAG ≤44.

In the **AN01.01.0011** study the randomised phase of the study analyses of efficacy variables showed no notable or statistically significant difference in favour of ethyl EPA. Analyses of the open-label data for patients treated up to 12-months showed a significant treatment effect with ethyl-EPA in the ITT population (with respect to TMS-4, TMS and maximal chorea score). This finding might however have been influenced by selection bias or bias due to knowledge of treatment during this study phase and, coupled with its post-hoc nature, can thus not be seen as conclusive.

Study **AN01.01.0012** demonstrated no differences between ethyl-EPA and placebo. A high placebo response was observed. The expected deterioration in motor function of HD patients given placebo only was not observed in this study. This finding does support the fact that the claimed long-term superiority of the ethyl-EPA treatment compared with placebo is not a consistent observation in all phase III studies.

Furthermore, results across studies are apparently inconsistent. The presented negative results can not be compensated on the basis of the presented post-hoc analyses including the longitudinal analysis which likewise shows no consistent results across studies LA01.01.0005, AN01.01.0011 and AN01.01.0012.

Finally, MRI brain imaging did not provide convincing measurable evidence of a positive effect of ethyl-EPA.

Thus, in conclusion, efficacy of ethyl-EPA in the claimed indication 'Long-term stabilisation of symptoms in patients with Huntington's disease' has not been sufficiently proven.

V.2 Risks

Ethyl-EPA products have been on the market for a number of years for use in peripheral vascular disease, hypercholesterolaemia and as an adjuvant treatment in secondary myocardial infarction. During this time no worrisome trends were seen.

The main AEs characteristic of ethyl-EPA are related to the gastrointestinal tract e.g. reflux, eructation, nausea, vomiting, distension, diarrhoea and constipation. These are characteristic of the omega-3 triglycerides, many of which are widely available as nutritional supplements. The most common AEs observed during the double-blind phase of the Applicant's studies were related to the gastrointestinal system with diarrhoea/loose stools being the most common. Thus there might be a slight risk of dehydration and, due to the oily nature of the product, a reduced uptake of fat-soluble vitamins.

There were no marked and clinically significant changes in the results of laboratory safety tests, vital signs or physical examination following treatment with ethyl-EPA.

It is widely accepted that ethyl-EPA in common with other omega-3 fatty acids can prolong the bleeding time when used in high dosage. This prolongation, when it occurs, generally remains within the normal range for man and there is little evidence that it is associated with adverse events. The slight excess of bleeding events in Japanese subjects with high background EPA levels of dietary origin [JELIS], has led to concerns over potential interactions with NSAIDs and anticoagulants/anti-platelet drugs. However no such evidence of significant interaction has been reported in Western subjects receiving a drug from either of these groups in conjunction with an EPA-containing product. A review of AE data of 44 subjects exposed to 4 g/day ethyl-EPA for up to 12 weeks in studies LA01.01.0001 and LA01.01.0002 revealed no apparent effect on bleeding time. Neither have such adverse events have been observed in clinical trials.

However, the interactions problem was insufficiently studied and in face of the rational for interactions with antiaggregant products and with anti-coagulants formal studies should be done. The product should not be used in patients susceptible to haemorrhages or with patients about to undergo major surgery.

From a pharmacokinetic point of view, there are hints towards possible CYP interactions/inhibition and renal/hepatic impairment. These issues were not studied adequately by the applicant in this submission.

V.3 Balance

Even if taking into consideration that orphan drug status has been granted for ethyl-EPA in the treatment of HD and that the medical need of effective treatment in patients with HD is high, efficacy of ethyl-EPA in the claimed indication 'long-term stabilisation of symptoms in patients with Huntington's disease' was not proven based on the submitted data. Thus, despite the reasonably favourable adverse-event profile, the use of ethyl-EPA can not be seen as beneficial.

V.4 Conclusions

The overall B/R of Ethyl eicosapent (Ethyl-EPA) 500 mg soft gelatin capsules is negative as no clear efficacy of the product in the treatment of HD was proven.