SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Depocyte. For information on changes after approval please refer to module 8.

1. Introduction

DepoCyte is a novel formulation of cytarabine (ara-C) encapsulated in multivesicular lipid particles that act as a slow release reservoir. It is intended for intrathecal administration for the treatment of lymphomatous meningitis. The following dose regimen is recommended.

- Induction therapy: 50 mg administered intrathecally (by lumbar puncture or intraventricularly via an Ommaya reservoir) every 14 days for 2 doses (weeks 1 and 3).

- Consolidation therapy: 50 mg administered intrathecally (by lumbar puncture or intraventricularly via an Ommaya reservoir) every 14 days for 3 doses (weeks 5, 7 and 9) followed by an additional dose of 50 mg at week 13.

- Maintenance therapy: 50 mg administered intrathecally (by lumbar puncture or intraventricularly via an Ommaya reservoir) every 28 days for 4 doses (weeks 17, 21, 25 and 29).

Lymphomatous meningitis occurs in up to a quarter of patients with Non-Hodgkin's Lymphoma (NHL), being more frequent in AIDS-related NHL than in non-AIDS NHL. Treatment of this complication aims at the palliation of its frequent symptoms, such as cranial nerve palsies, focal sensory and/or motor deficits, headache and encephalopathy.

Ara-C is an active agent against NHL and, following intrathecal administration, is known to induce responses in patients with lymphomatous meningitis. Ara-C is a cell-cycle phase specific antimetabolite that inhibits DNA synthesis. It is most effective in the clearance of the CSF of malignant cells when it is maintained at cytotoxic concentrations in the environment of the malignant cells for many days.

2. Chemical, pharmaceutical and biological aspects

Composition

DepoCyte is a sterile, injectable suspension of the antimetabolite ara-C encapsulated into multivesicular lipid-based particles (DepoFoam) for sustained release. Each vial of DepoCyte contains a suspension of 50 mg encapsulated ara-C in 5 ml of solution.

The primary components of the container-closure system are
- 5 ml, Ph.Eur. Type I flint glass vials, 13 mm opening
- 13 mm, grey, butyl rubber stoppers with fluoresin or Teflon coated product contact surfaces
- Aluminium flip off seals

Active substance

The active substance is cytarabine (ara-C), which is listed in the current versions of the USP and Ph. Eur.

The applicant has presented a harmonised USP/Ph. Eur. specification. Tests include determination of residual methanol, ethanol and acetonitrile, determination of 5-methylcytarabine and bacterial endotoxins. The limits for residual solvents are within the limits set out in the ICH guideline on residual solvents.

Batch analysis data were provided on ten consecutive batches of active substance. The results confirm the consistency and uniformity of the synthesis. The only related substances observed were uracil arabinoside and 5-methylcytarabine. Ethanol was the only organic solvent present.

Primary stability data were generated on five batches of active substance. Up to 48 months data were available. No significant deviations from initial values were noted. The data provided support the proposed retest period of 36 months.

Other ingredients

Cholesterol, sodium chloride and water for injection are described in the PhEur and conform to these specifications. The specifications for dioleoylphosphatidylcholine (DOPC) and dipalmitoylphosphatidyl-glycerol (DPPG) are acceptable.

Product development and finished product

The drug encapsulating particles (DepoFoam) are a proprietary drug delivery system that aims to provide sustained release of therapeutic compounds. The microscopic spherical particles are composed of numerous non-concentric internal aqueous chambers separated by bilayer lipid membranes. The components of DepoFoam particles are synthetic analogues of common, naturally occurring lipids. The DepoFoam formulation of ara-C (DepoCyte) is stored under refrigeration in a ready-to-use injectable form.

DepoFoam particles release the drug over a period of time which can be modified by the lipid composition, chemical properties of the drug to be encapsulated, and manufacturing parameters used in production. The drug may be released from DepoFoam particles by erosion and/or reorganisation of the lipid membranes of particles *in vivo*.

DepoFoam particles are different from other lipid-based drug delivery systems such as unilamellar and multilamellar liposomes. The main structural difference is that, in contrast to unilamellar liposomes, multivesicular liposomes (MVL) contain multiple aqueous chambers per particle. In contrast to multilamellar liposomes, the multiple aqueous chambers in MVL are non-concentric. The presence of internal aqueous chambers may serve to confer increased mechanical strength to the vesicle. The multivesicular nature of MVL also indicates that, unlike conventional unilamellar liposomes, a single breach in the external membrane of an MVL will not result in total release of internal aqueous contents.

The manufacturing process, used to produce DepoCyte clinical product to support the phase III study, was established at an appropriate scale for clinical supply. This process was compared with the manufacturing process proposed for the commercial production by means of a bioequivalence study. The composition of DepoCyte used during clinical trials is the same as that intended for commercial distribution.

The basic steps in the process and the composition of the chemicals used in production of DepoCyte have not changed during the development and scale-up of the manufacturing process. Changes in the process relate to the equipment, the scale and the site of manufacture of the product.

An aseptic process that is totally enclosed manufactures DepoCyte. The product suspension is filled into vials and sealed under aseptic conditions.

Vials and stoppers used to fill the product are cleaned, then depyrogenated (vials), or sterilized by autoclaving (stoppers). Filling equipment that contacts the product is sterilized by autoclaving. Sterilization and depyrogenation component validation has been performed.

Validation of the process has been performed on three nominal batches and in three worst case batches.

The product is being manufactured in a facility that holds the necessary Manufacturing Authorisation (see Annex II of the Opinion).

Determination of sterility and monitoring of bacterial endotoxins is performed according to the Ph. Eur. Impurity limits in the product specification are justified by toxicology studies.

Initial release data from the 10x scale validation batches were provided. Data on 13 commercial scale batches have also been provided. All results indicate a reliable and consistent performance of the product in clinical use.

Stability of the product
Data were generated on nine batches. Photostability studies were carried out on a single (10x) batch. Twenty-four months data were available. The results support a shelf-life of 24 months.

Discussion on chemical, pharmaceutical and biological aspects
In summary, the documentation of substances, materials, methods of production as well as the quality controls is sufficient to ensure a product of appropriate and consistent quality. Information has been provided in the dossier demonstrating that the medicinal product is made in compliance with the CPMP Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products.

3. Toxico-pharmacological aspects

Ara-C is an analogue of deoxycytidine and has multiple effects on DNA synthesis. It undergoes phosphorylation to form ara-CTP, which competitively inhibits DNA polymerase α in opposition to the normal substrate deoxycytidine 5'-triphosphate (dCTP). The effects of ara-C on DNA polymerase extend not only to semiconservative DNA replication, but also to DNA repair. More importantly, ara-C is incorporated into DNA. This feature is the major cytotoxic lesion in ara-C-treated cells. Drugs like aphidicolin which prevent the ara-C incorporation into DNA also block its cytotoxicity.

Pharmacodynamics

***In vitro* studies**
The clinical efficacy of ara-C is dependent on the dose and on the schedule because of its short biological half-life. Ara-C completely inhibited multiplication of mouse L-cells in culture during an exposure interval from 4 to 28 hours but had no effect on cell viability. At a higher concentration of it slowly decreased the survival. Also in cultured human myeloid leukaemia cells, B-lymphoid leukaemia cells and T-lymphoid leukaemia cells, the concentrations of ara-C inducing a 50% cell kill over a 48 hours exposure were in the range of 0.3, 2 and 0.02 μM respectively. In cultured normal human bone marrow cells, after 24 hours of incubation, the IC_{50} of ara-C was 1.7 μM and was decreased to 0.008 μM when the incubation time was prolonged up to 5 days.

The dependence of the cytotoxic effect of ara-C on the schedule has been further elucidated by studies of cultured bone marrow cells from untreated patients with acute myeloid leukaemia, where it was observed that cytotoxicity increased when cells were exposed for long periods, thus allowing lower concentrations to be effective.

***In vivo* studies**
No pharmacodynamic studies with DepoCyte were conducted related to the proposed indication. However, some studies using ara-C entrapped in multivesicular liposomes are available and were related to the subsequent development of DepoCyte.

The i.p. administration of ara-C in multivesicular liposomes has been shown to prolong survival in mice inoculated with L1210 cells.

The better cytotoxic profile suggested by these studies for DepoCyte, coupled to the already established use of the drug in the treatment of haematologic malignancies in humans, justified the subsequent development of DepoCyte for intrathecal administration for the treatment of neoplastic meningitis of patients with solid tumours, taking into account the possibility that effective ara-C levels could persist in the CSF and intrathecal tissues without significant systemic exposure, at a dose lower than that used for systemic administration.

Drug interactions
Although drug interactions have been reported following the IV administration of ara-C, the difference in clearance of ara-C from the CSF and plasma is so large that no clinically significant levels of ara-C

are found in the plasma. Likewise, the medicinal products for which interactions have been reported generally do not cross the blood-brain barrier well enough to interact significantly with ara-C.

Pharmacokinetics

Introduction
Seven pharmacokinetic studies were conducted in rodents and primates. Two of these studies used preliminary formulations. Additional studies examined and compared the intrathecal pharmacokinetics of ^{3}H-cytarabine and ^{14}C-DOPC with those of standard ara-C.

Absorption and Distribution
After lumbar injection of DepoFoam-encapsulated ^{3}H-ara-C in rats, the radiolabel rapidly distributed throughout the neuraxis with peak levels at 160 minutes post-dose. Cisternal-to-lumbar CSF ratios of the radiolabel were < 1 indicating that the active substance preferentially resided near the injection site. The cisternal/lumbar ratio was greater for ^{3}H (active substance) than for ^{14}C (lipid) which provided evidence that the free active substance has greater mobility along the neuraxis than the DepoFoam particles. Similar biphasic CSF and plasma kinetic profiles of ^{3}H and ^{14}C indicated that the release of active substance was directly related to the breakdown of the DepoFoam particles. The ^{3}H label distributed into the systemic circulation after release of the DepoFoam particles.

After lumbar intrathecal injection of ara-C encapsulated into DepoFoam prepared with ^{14}C-DOPC, the ^{14}C label rapidly distributed throughout the neuraxis, preferentially residing near the injection site. About 10% of the radiolabel was incorporated into CNS tissues early post-dose and remained stable still being present at 504 days post-dose. The amount incorporated into CNS tissues decreased from the injection site, which was most likely driven by the high concentration gradient achieved immediately post-dose. The detection of ^{14}C in the plasma throughout the study indicated that the DepoFoam particles break down in the intrathecal space and lipids are liberated and apparently cleared from the CNS.

Metabolism
No formal metabolism studies were conducted with DepoFoam-encapsulated ara-C. However, data was obtained from the double-labelled studies in the rat. The disappearance of ^{3}H radiolabel from the CSF and CNS tissues was associated with a concomitant increase in the amount of ^{3}H label in the plasma. The moiety(ies) bearing this label were not characterised.

The presence of ^{14}C as phospholipid, monoglycerides and/or fatty acids in plasma indicated that DOPC or the hydrolysis products released during DepoFoam particle breakdown were cleared from the CNS into the periphery. The lipids might be incorporated into standard catabolic pathways.

Excretion and half-life
Data from the double-labelled studies in the rat indicated that following its release from the DepoFoam matrix, ara-C is cleared from the CSF. Like standard ara-C it may be removed from the central compartment by bulk flow with little metabolism. Once in the systemic circulation the ^{3}H label appeared to be primarily cleared by the kidneys as evidenced by the accumulation of ^{3}H label in the urine.

Concerning DOPC, a large part of the applied ^{14}C dose could not be accounted for by the end of the study. About 10% was incorporated into CNS tissues, there was minor incorporation of label into peripheral tissues, no excretion in faeces and <6% excreted in the urine. Most of this radiolabel might eventually have been expired as $^{14}CO_2$.

In the rat the half-life of ara-C within the cranial compartment following a 1 mg dose was 148 hours, whilst that of an equal dose of standard ara-C was 2.7 hours. Free ara-C concentrations in the CSF remained above the estimated minimal cytotoxic level of 0.1 µg/ml for 16 days post-dose with of DepoFoam-encapsulated ara-C.

In a similar study in the monkey dosed with DepoFoam-encapsulated ara-C at 2 mg, ara-C concentrations in lumbar CSF decreased biexponentially with initial and terminal half-lives of 14.6 and 156 hours respectively whilst that of standard ara-C was 44 minutes. CSF concentrations of the active substance remained above the minimal cytotoxic level for more than 672 hours post-dose.

In more recent intrathecal dosing studies employing clinical- and commercial-scale DepoFoam-encapsulated ara-C in monkeys, elimination phase half-lives were 16.0 to 21.8 hours for ara-C in CSF

following intrathecal administration of a single 6 mg dose. As described above, concentrations of the active substance decreased biexponentially with an initial rapid decline over the first 12 to 24 hours followed by a slower decline over the next few days. Mean residence times in the CSF ranged from 3 to 5.6 hours; the active substance was no longer detectable by 120 hours post-dose.

Drug interactions
Following intrathecal administration, no clinically significant levels of ara-C have been found in the plasma. Medicinal products for which interactions have been reported generally do not cross the blood-brain barrier well, therefore the likelihood of interactions is small.

Toxicology

Single-dose toxicology
Two studies were conducted in Rhesus monkeys. In both studies of DepoFoam-encapsulated ara-C was administered via the intrathecal route. Although both studies were conducted in 1995 they were not in accordance with GLP.

The purpose of the first study was to establish the MTD, to gather preliminary toxicokinetic information and to establish dexamethasone dosing (to be used to alleviate any inflammatory responses due to the long duration of ara-C exposure) for the subsequent multi-dose study. DepoFoam-encapsulated ara-C was administered by bolus injection and/or infusion. A dose of 5 mg was well tolerated, at 10 mg transient tremors and convulsion were seen, and at 15 mg most animals developed stiffness of back and hypoactivity within 10 days of dosing. One animal, dosed at 20 mg, developed acute inflammation of the meninges in association with a catheter infection.

The purpose of the second study was to assess the acute toxicity and to gather toxicokinetic data following a MTD dose which was considered to be 10 mg based on the results of the first study. A dose of 10 mg was administered by infusion, followed after a treatment-free period by another dose of 10 mg by slow bolus injection. Overt signs of toxicity were limited to a stiffened back in the lumbar area. Slow bolus injection resulted in consistently greater CSF ara-C levels than infusion.

Repeated-dose toxicology
Eighteen Rhesus monkeys were treated intrathecally by infusion. The doses of DepoFoam-encapsulated ara-C were selected on the basis of the results of the single dose study. Each animal received a total of 4 doses of test article (1 dose/cycle, 14 day cycle). Dexamethasone was co-administered to all animals. Animals were euthanised 14 days after the fourth dose except for 1 male and 1 female in the vehicle and high dose of DepoFoam-encapsulated ara-C treatment groups which constituted the recovery groups and which were euthanised 93-202 days after the fourth dose.

Overt signs of toxicity, limited to the group receiving the highest dose of DepoFoam encapsulated ara-C, consisted of transient recumbency and back stiffness in 2/6 animals. Periodic decreases in food consumption occurred in both of the DepoFoam-encapsulated ara-C treated groups, although this did not produce a significant effect on body weight.

The most notable histopathological findings occurred in all animals treated with DepoFoam particle based materials and was characterised by meningeal inflammation and/or astrocytic activation in brain and/or spinal cord tissues. Meningeal inflammation in DepoFoam control or of DepoFoam-encapsulated ara-C treated animals was slight in severity and diffusely spread throughout the spinal column. No evidence of meningeal inflammation was reported for DepoFoam or of DepoFoam-encapsulated ara-C treated animals following the treatment-free period.

Genotoxicity
Ara-C has been shown to be mutagenic and clastogenic *in vitro* and *in vivo*.

Carcinogenicity
Although there was no evidence of carcinogenicity in rodent studies, antimetabolites such as ara-C may act as co-carcinogens. It is likely that DepoCyte will have the mutagenic and carcinogenic potential of ara-C.

Reproduction toxicity
Ara-C is a developmental toxicant and a teratogen in various species and several cytarabine-associated peri- and post-natal toxicities have been reported. Therefore it is likely that DepoCyte would have

similar adverse effects on reproduction, although systemic exposure to ara-C following the proposed therapeutic use may be very small.

Local tolerance
Local tolerance testing formed part of the toxicity studies conducted using the intrathecal route. No experimental data have been specifically generated.

Special toxicity studies
The particle components of the DepoFoam matrix are synthetic analogues of naturally occurring lipids. The safety of DOPC may be supported by the extensive toxicology database available on highly purified soya phosphatidylcholine. This compound was of low toxicity by several routes of administration in several species. However, the intrathecal route was not tested. Concerning DPDG the available literature indicated that liposomes formulated with negatively charged phospholipids such as DPPG were well tolerated even at high doses when administered i.v. to mice. Again no information on the effects of intrathecal administration is available.

Environmental Risk Assessment
Ara-C is extensively metabolised by patients. A large part (80%) of the administered dose is found in the urine by 24 hours. Approximately 90% of the urinary output is the inactive metabolite 1-β-D-arabinofuranosyluracil (ara-U). Any discharge to aquatic or terrestrial ecosystems is minimal.

Discussion on toxico-pharmacological aspects
The preclinical package of studies conducted with of DepoFoam-encapsulated ara-C was limited. The product contains three novel lipid excipients (triolein, DOPC and DPPG).

The pharmacokinetics of DOPC are not fully known. A large part of the radioactivity appeared to be unaccounted for, and might ultimately be expired as radiolabelled CO_2.

The number of animals used in the toxicology studies was very limited, and in the repeat dose toxicity studies the maximum number was four, and not nine, as intended for clinical use. This has been justified by the fact that the applied dose of 10 mg/animal is equivalent to 100 mg/patient or approximately 2 times the studied clinical dose. Based on this exposure, 4 cycles of treatment were considered sufficient.

Of concern is that intrathecal administration of DepoFoam caused meningeal inflammation, which was evident after only four treatments. This is particularly relevant in view of the concerns about the occurrence of arachnoiditis during clinical use. However, the meningeal inflammation appeared to be fully reversible after a lengthy treatment-free recovery period.

4. Clinical aspects

The clinical data consisted of phase I, phase III and phase IV data with DepoCyte in various patient populations. The main clinical data consisted of a series of 35 patients from a phase III trial of DepoCyte *versus* a standard formulation of ara-C for the intrathecal treatment of lymphomatous meningitis. Overall, 237 patients were entered in phase III and phase IV studies. Pharmacokinetic data were obtained as part of a phase I study (n=19) and 2 population pharmacokinetic studies (n=11 and 13 for the US and the European study, respectively).

Clinical pharmacology

Pharmacodynamics
Ara-C is a well-known S phase-specific antimetabolite that, after intracellular activation to ara-CTP, inhibits DNA synthesis by competitively binding DNA polymerase; ara-C is also incorporated into the DNA, impairing repair mechanisms. The bone marrow and the gastrointestinal epithelium are targeted by ara-C with ensuing myelossupression and nausea, vomiting and mucositis. It is active in rapidly proliferating lymphatic or haematological malignancies. However, it is believed to be less active in solid tumours.

Pharmacokinetics

The pharmacokinetics of ara-C were investigated in a phase I dose-ranging study after intraventricular and intralumbar administration of DepoFoam-encapsulated ara-C in patients with neoplastic

meningitis. Nineteen patients with haematological and non-haematological neoplasia and a pathological diagnosis of leptomeningeal spread were enrolled.

A fixed dose of 50 mg was selected on the basis of the phase I study, which concluded that the maximum tolerated dose was 75 mg, and that dexamethasone should be given for 5 days with DepoCyte in all future studies.

Ara-C was measured in CSF samples obtained before each injection and at several time points after the injection. These samples were analysed for free and encapsulated ara-C and for ara-U. Ara-C and ara-U levels were also measured in plasma samples by HPLC. The maximum tolerated dose was defined as the one that produced grade II or worse toxicity in the CNS, according to the CALGB criteria, or grade III in any other organ system.

In addition an intrathecal PK substudy of the phase III trial was performed to determine the pharmacokinetics of ara-C after the administration of 50 mg of DepoCyte via the intra-ventricular *versus* the intra-lumbar routes in patients with neoplastic meningitis as well as to compare the PK of two different formulations of DepoCyte.

Distribution and half-life

Following intrathecal DepoCyte administration in patients, either by injection into the lumbar sac or through an intraventricular reservoir, peaks of free ara-C were observed within 5 hours in both the ventricular and lumbar sac. These peaks were followed by a biphasic elimination profile consisting of an initial sharp decline and subsequent slow decline with a terminal phase half-life of 100 to 263 hours over a dose-range of 12.5 mg to 75 mg. In contrast, intrathecal administration of 30 mg free ara-C has shown a biphasic CSF concentration profile with a terminal phase half-life of about 3.4 hours.

Pharmacokinetic parameters of intrathecal administration of DepoCyte (75 mg) in neoplastic meningitis patients following injection into either the lumbar sac or through an intraventricular reservoir suggest that exposure to the drug in the ventricular or lumbar spaces is similar regardless of the route of administration.

Compared to free ara-C, DepoCyte increases the biological $t_{1/2}$ by a factor of 27 to 71 depending upon the route of administration and the compartment sampled. Encapsulated ara-C concentrations and DepoFoam particle counts followed a similar distribution pattern. AUCs of free and encapsulated ara-C after ventricular injection of DepoCyte appeared to increase linearly with increasing dose, indicating that the release of ara-C from DepoCyte and the pharmacokinetics of ara-C are linear in human CSF.

Systemic exposure to ara-C was determined to be negligible following intrathecal administration of 50 and 75 mg of DepoCyte.

Metabolism and elimination

The primary route of elimination of ara-C is metabolism to the inactive compound ara-U, (1-β-D-arabinofuranosyluracil or uracil arabinoside) followed by urinary excretion of ara-U. In contrast, conversion to ara-U in the CSF is negligible after intrathecal administration because of the significantly lower cytidine deaminase activity in the CNS tissues and CSF. The CSF clearance rate of ara-C is similar to the CSF bulk flow rate of 0.24 ml/min.

Drug interaction studies

Interaction studies using DepoCyte have not been conducted. Several drug interactions have been noted in patients receiving ara-C, including inhibition of gentamicin and flucytosine activity and reduced absorption of digoxin. DepoCyte is likely to have a similar drug interaction profile to the standard agent; however, because plasma levels are negligible following intrathecal DepoCyte administration, the risk of systemic interactions appears small.

Clinical efficacy

The main clinical data are derived from a randomised clinical trial of DepoCyte *versus* a standard formulation of ara-c for the intrathecal treatment of lymphomatous meningitis. The main clinical data submitted with the original application consisted of the data for 28 patients with lymphomatous meningitis. During the evaluation, an update was provided and in total, data on 35 patients with lymphomatous meningitis from the phase III trial were presented. Supportive data was provided from a small subgroup of lymphomatous meningitis patients (n=6) included in the phase I study.

The phase III trial in lymphomatous meningitis was one of three phase III trials conducted with DepoCyte. The remaining two studies were a phase III trial of DepoCyte *versus* methotrexate in patients with solid tumours (n=61 with 31 and 30 patients randomised to DepoCyte and methotrexate, respectively) and a phase III trial of DepoCyte *versus* a standard formulation of ara-c in leukaemic meningitis, which was terminated prematurely (n=7).

Data from a Phase IV study in solid tumour neoplastic meningitis were also provided (n=89 and n=110 for the initial application and the update, respectively).

Main clinical study

Patients and methods

Eligibility criteria included histologically proven diagnosis of lymphoma (AIDS or non-AIDS), positive cytology in CSF sampled from the lateral ventricle or the lumbar sac, no compartmentalisation of CSF flow, age ≥ 3, expected survival ≥ 2 months and recovery from toxicity due to prior intrathecal treatment. Prospective stratification according to AIDS-related *versus* non-AIDS-related lymphomatous meningitis was implemented.

Patients were randomised to receive DepoCyte 50 mg once every 2 weeks or free ara-C 50 mg twice a week for 1 month (induction). Patients whose CSF cytology converted to negative and who did not have neurologic progression received an additional 3 months of consolidation therapy. For patients randomised to DepoCyte, consolidation therapy consisted of DepoCyte 50 mg every 14 days for one month and then monthly for 2 months. For patients randomised to the control arm, consolidation treatment consisted of unencapsulated ara-C 50 mg once weekly for one month followed by 50 mg every 2 weeks for two months. Patients who remained in remission at the end of consolidation treatment were to continue for an additional four months of maintenance treatment. Maintenance treatment consisted of DepoCyte 50 mg monthly for 4 months, or free ara-C 50 mg monthly for 4 months, for the two treatment arms, respectively.

Concomitant systemic chemotherapy or limited field radiotherapy were allowed. Local irradiation had to be given for symptomatic or bulky CNS disease and concurrent partial brain or limited-field spinal radiation therapy was strongly recommended for radiologically visible CNS disease. Whole brain or cranio-spinal irradiation during the induction, consolidation and maintenance periods was prohibited.

The primary efficacy endpoint was response defined as confirmed cytological conversion (complete cytological response according to central cytology review) and lack of neurologic progression evaluation at the time of assessment (4 weeks after the beginning of treatment). Central cytopathology review was blinded to study treatment and chronology of CSF samples and was carried out on all CSF cytology slides after study completion. The primary analysis of response rate was carried out in the intent-to-treat population (all randomised patients).

Other endpoints investigated were duration of response and progression-free survival, neurological signs and symptoms, Karnofsky performance status, quality of life (QOL) and overall survival. QOL assessments used the FACT-CNS instrument and Mini Mental State examination. Exploratory analyses of quality of life were performed using Q-TWIST (Time without symptoms and toxicity) and QOL-adjusted survival analysis methodology.

The trial was performed according to GCP standards and agreed international ethical principles.

Results

The pre-specified sample size was 40 patients. Due to insufficient recruitment at the end of the recruitment period, an unplanned interim analysis was carried out and the results were submitted with the marketing authorisation application. The interim analysis was based on 28 patients (14 *versus* 14 for DepoCyte *versus* ara-C respectively). Thereafter, 7 additional patients completed treatment and updated clinical efficacy results were provided (final analysis). In total, the study enrolled 35 patients (18 *versus* 17 for DepoCyte *versus* ara-C respectively).

In the entire population (n=35), 8 patients in the DepoCyte arm and 5 in the ara-C arm received concurrent systemic chemotherapy. Also, 4 patients in the DepoCyte arm and 1 in the ara-C arm received concurrent CNS radiotherapy. One patient who obtained a complete response with DepoCyte received concurrent whole brain irradiation for CSF flow block (despite whole brain irradiation being

prohibited by the protocol). Data on the extent of CNS irradiation treatments prior to or during chemotherapy were lacking.

In the interim analysis, response rate was 10/14 (71%, 95% binomial confidence interval: 42, 92) in the DepoCyte arm *versus* 2/14 (14% patients, 95% binomial confidence interval: 2, 43) in the unencapsulated ara-C arm and a statistically significant association between treatment and response was observed (Fisher's exact test p-value = 0.006).

In the final analysis, response rate was 13/18 (72%, 95% binomial confidence interval: 47, 90) in the DepoCyte arm *versus* 3/17 (18% patients, 95% binomial confidence interval: 4, 43) in the unencapsulated ara-C arm and a statistically significant association between treatment and response was observed (Fisher's exact test p-value = 0.002). Response scored on the basis of the local institutional non-blinded cytologist's reading was 16/18 (89%) in the DepoCyte arm *versus* 6/17 (35%) in the free ara-C arm. Duration of response was similar across treatment arms. The median duration of response was 34 *versus* 16 days for DepoCyte *versus* ara-C, respectively.

Neurological progression-free survival was not statistically significantly different between the two treatment arms (n=35; median: 77 *versus* 48 days for DepoCyte *versus* ara-C, respectively). Cytological progression-free survival was also not statistically significantly different across treatment arms (n=28; median: 61 *versus* 33 days for DepoCyte *versus* ara-C, respectively). Overall survival was similar across treatment arms (n=35; median: 97 *versus* 96 days for DepoCyte *versus* ara-C, respectively).

Karnofsky performance status, Mini Mental State and the FACT-CNS instrument did not show statically significant differences between the groups. No statistically significant difference in time without toxicity due to either treatment or progression was noted by Q-TWIST analysis (n=35; median: 115 *versus* 68 days for DepoCyte *versus* ara-C, respectively).

Other clinical efficacy data

From the supportive clinical data submitted, 3 out of 6 patients with in lymphomatous meningitis showed a complete cytological response. No patients showed improvements in neurological status. The median survival time for patients with lymphoma was 86 days.

Discussion on clinical efficacy

A statistically significant difference in favour of DepoCyte for the primary efficacy endpoint is claimed based on the the open label, randomised trial comparing DepoCyte and conventional unencapsulated ara-C in 28 patients with lymphomatous meningitis. Similar results are claimed on the basis of the final analysis carried out in 35 patients.

Despite the claimed statistical significance of the observed results, due to the small sample size and the methodological drawbacks of unplanned analyses, the main clinical trial in lymphomatous meningitis fails to show any compelling evidence of superior clinical efficacy of DepoCyte compared to conventional ara-C.

A low response rate for the standard arm was noted compared to historical series. It is possible that this could be at least in part explained by the strict response criteria used in the study. No apparent pattern in response by concomitant treatments was noted.

It is acknowledged that, despite the small sample size, this is the largest randomised trial ever performed in this patient population. In this population, DepoCyte produced a high response rate according to rigorously defined criteria and independent central review of responses was carried out. Although strong evidence to support a claim of superiority of DepoCyte compared to conventional unencapsulated ara-C is lacking, the observed response rate may indicate that inferiority of DepoCyte is unlikely.

More importantly, DepoCyte has a more convenient schedule of administration compared to conventional unencapsulated ara-C, as it reduces the need for multiple injections and this may have a favourable impact on quality of life. Other intrathecal chemotherapy programs commonly used in Europe require 2-3 lumbar punctures each week.

Clinical safety

The safety data concerning DepoCyte mainly consist of data from patients who received the 50 mg dose of DepoCyte. Additional safety data were obtained from 9 patients who received subcutaneous DepoCyte, and 9 other patients who received other doses than 50 mg DepoCyte (in the pilot study).
In the main clinical study, 17/18 and 16/17 patients actually started treatment with DepoCyte and unencapsulated ara-C, respectively. In the phase III trial of DepoCyte *versus* methotrexate in patients with solid tumours (n=61), 29/31 and 30/30 actually started treatment with DepoCyte and methotrexate, respectively. Adverse events were graded according to CALGB Expanded CTC criteria. The total number of patients actually treated with DepoCyte and the total number of cycles administered in the various studies included in the safety database are summarised in Table 1.

Table 1. Total number of patients actually treated with DepoCyte and total number of cycles administered in Phase III, IV and in the population pharmacokinetics studies

	Total No. patients	Total No. cycles
Lymphomatous meningitis	17	89
Solid tumour meningitis	29	102
Leukaemic meningitis	4	18
Phase IV trial	110	386
US pharmacokinetics trial	11	44
European pharmacokinetics trial	13	50
Total	184	689

Adverse events, serious adverse event/deaths

Treatment-related adverse events are shown in Table 2. In the main clinical study of patients with lymphomatous meningitis, the more frequently observed Grade 3-4 treatment-related adverse events for DepoCyte (total number of cycles = 89) were headache, which was observed in 5 cycles (5.6 %), arachnoiditis in 4 cycles (4.5%) and neutropenia in 3 cycles (3.3%). Other treatment-related adverse events included agitation, abnormal CSF chemistries, confusion, fever, somnolence, thrombocytopenia, each observed in 2 cycles (2.2%), whilst asthenia, hydrocephalus, hypestesia, pain, vomiting were each observed in 1 cycle (1.2%). For unencapsulated ara-C (n=56.25), the observed Grade 3-4 treatment-related adverse events were asthenia, headache, somnolence, thinking abnormal, each observed in 1 cycle (1.8%).

Table 2. Treatment-related adverse events of any grade per cycle (Phase III study in lymphomatous meningitis)

	DepoCyte Total No. of cycles=89 No. of cycles (%)	Ara-C Total No. of cycles=56.25 [a] No. of cycles (%)
Abdominal pain	2 (2.2)	0 (0)
Agitation	4 (4.5)	0 (0)
Anaemia	0 (0)	2 (3.6)
Anorexia	2 (2.2)	0 (0)
Arachnoiditis [b]	5 (5.6)	0 (0)
Asthenia	2 (2.2)	5 (8.9)
Cerebrospinal fluid abnormal	2 (2.2)	0 (0)
Confusion	6 (6.7)	0 (0)
Deafness	2 (2.2)	0 (0)
Diarrhoea	0 (0)	2 (3.6)
Dizziness	2 (2.2)	0 (0)
Fever	7 (7.9)	3 (5.3)
Headache	21 (23.6)	2 (3.6)
Hydrocephalus	2 (2.2)	0 (0)
Hypesthesia	3 (3.4)	0 (0)
Nausea	8 (9.0)	2 (3.6)
Neutropenia	3 (3.4)	0 (0)
Pain	4 (4.5)	2 (3.6)
Paresthesia	0 (0)	2 (3.6)
Peripheral oedema	2 (2.2)	0 (0)
Somnolence	6 (6.7)	2 (3.6)
Thinking abnormal	2 (2.2)	0 (0)
Thrombocytopenia	2 (2.2)	0 (0)
Vertigo	2 (2.2)	0 (0)
Vomiting	7 (7.9)	0 (0)

[a] Cycle length definition: Cycle length was 2 weeks during which the patient received either 1 dose of DepoCyte or 4 doses of ara-C or methotrexate. Ara-C and methotrexate patients not completing all 4 doses are counted as a fraction of a cycle.

[b] Arachnoiditis: defined according to individual physician's criteria.

Drug-induced arachnoiditis, a syndrome manifested primarily by headache, nausea, vomiting, fever, neck rigidity, neck or back pain, meningism, CSF pleocytosis, with or without altered state of consciousness was the most common adverse event. A more detailed analysis of this syndrome, using an objective definition was produced (Table 3). Arachnoiditis was defined as the occurrence, within 4 days of the injection, of either:

- Neck rigidity, neck pain or meningism, *or*
- At least two of the following at the same time: nausea, vomiting, headache, fever, back pain or CSF pleocytosis.

Arachnoiditis was graded based on the most severe of the constituent adverse events.

The proportion of patients who had at least one episode of arachnoiditis in all trials of DepoCyte was about 49% of patients treated with DepoCyte, compared to about 33 – 42% of patients who received conventional therapy. In 19% of patients treated with DepoCyte, possible or definite cases of serious arachnoiditis associated with alterations in level of consciousness were observed. On a per-cycle basis, there was no difference in overall occurrence of grade 3-4 arachnoiditis across treatment arms in the main clinical study (Table 3). A retrospective analysis suggested that use of dexamethasone reduced the incidence of arachnoiditis.

Table 3. Arachnoiditis [a] per cycle

	Lymphomatous Meningitis (Phase III)		Solid Tumour Meningitis (Phase III)		Solid Tumour Meningitis (Phase IV)
	DepoCyte	Ara-C	DepoCyte	MTX	DepoCyte
Total No. of cycles [b]	**89**	**56.25**	**102**	**69.5**	**386**
Grade 3-4	6%	7%	4%	3%	8%
Any Grade	18%	16%	23%	19%	17%

[a] Arachnoiditis: objective definition in the text.

[b] Cycle length definition: see table 2.

Another analysis focussed on other symptoms of meningeal irritation and included any adverse events, which could possibly be clinical representations of meningeal irritation in the pooled patient population (Table 4).

Table 4. Adverse events possibly reflecting meningeal irritation per cycle (in patients who started protocol treatment in the Phase III, IV and in the population pharmacokinetics studies)

Adverse Event	DepoCyte Phase III, IV and population pharmacokinetic studies	Ara-C Phase III study in Lymphomatous Meningitis	Methotrexate Phase III study in Solid Tumour Meningitis
Total No. of cycles [a]	**689**	**56.25**	**69.5**
Headache	25%	12%	22%
Nausea	19%	16%	17%
Vomiting	17%	16%	24%
Fever	13%	21%	12%
Back pain	11%	9%	14%
Convulsions	7%	2%	9%
Neck pain	5%	4%	3%
Neck rigidity	3%	4%	0%
Hydrocephalus	2%	0%	3%
Meningism	1%	4%	0%

[a] Cycle length definition: see Table 2.

As anticipated in this patient population, serious adverse events were common and occurred with a similar frequency in patients receiving either DepoCyte, conventional unencapsulated ara-C, or methotrexate. One treatment-related death was reported from the pilot study. This was associated with encephalopathy developing 36 hours after an intraventricular dose of 125 mg DepoCyte. One possibly treatment-related death, involving status epilepticus, was reported from the PK study.

Discussion on clinical safety

Treatment-related arachnoiditis was the most common adverse event although the precise relationship with treatment was difficult to assess in this patient population. The incidence of arachnoiditis was similar in patients treated with DepoCyte *versus* conventional ara-C. In addition, the occurrence of arachnoiditis did not result in DepoCyte treatment discontinuation. The arachnoiditis associated with DepoCyte was considered to be generally mild, reversible and easily managed with steroids.

5. Overall conclusions, benefit/risk assessment and recommendation

Quality
The documentation of substances, materials, methods of production as well as the quality controls is sufficient to ensure a product of appropriate and consistent quality. In conclusion, the quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC.

Pre-clinical pharmacology and toxicology

Intrathecal administration of DepoFoam caused meningeal inflammation, which was evident after only 4 treatments. This was of concern in view of the occurrence of arachnoiditis during clinical use. However, the meningeal inflammation appeared to be fully reversible after a lengthy treatment-free recovery period.

Clinical Efficacy

The main clinical trial in lymphomatous meningitis failed to show any compelling evidence of superior clinical efficacy of DepoCyte compared to conventional unencapsulated ara-C. However, the observed response rate indicated that inferiority of DepoCyte is unlikely. More importantly, however, DepoCyte has a more convenient schedule of administration compared to conventional ara-C. Particularly, it reduces the need for multiple injections and this may impact quality of life favourably.

Clinical Safety

Like other intrathecally administered agents, DepoCyte produced some degree of meningeal irritation which, however, was manageable, did not lead to treatment discontinuation. Arachnoiditis was the most common adverse event observed with DepoCyte. However, the arachnoiditis associated with DepoCyte was considered to be generally mild, reversible and manageable. The incidence of arachnoiditis was similar in patients treated with DepoCyte *versus* conventional ara-C and did not result in protocol treatment discontinuation. In conclusion, from the clinical safety data presented DepoCyte did not show new toxicity compared to standard ara-C.

Benefit/risk assessment

The main clinical trial in lymphomatous meningitis failed to show compelling evidence of superior clinical efficacy of DepoCyte compared to conventional ara-C. Although a statistically significant association between response and treatment was noted, results were difficult to interpret, due to methodological difficulties related with unplanned interim analyses. However, in an oral explanation, the applicant provided some justification for this methodological approach, based on the difficulties of completing the intended recruitment due to the complexity of performing a randomised study with intrathecal regimens in this patient population. Also, despite the interim analysis, the population included in the final analysis was close to the intended target recruitment. In addition, the randomised lymphomatous meningitis trial is the largest that has ever been completed with intrathecal treatment in this setting.

The CPMP concluded that, from a point of view of clinical efficacy, enough evidence had been submitted to confirm an at least similar activity compared to standard ara-C. Standard ara-C treatment was considered to be an adequate reference treatment in this patient population, although the extent to which this treatment is established in the management of this rare condition remained a matter of debate. In view of the more convenient schedule of administration of DepoCyte, compared to conventional unencapsulated ara-C, the clinical efficacy data presented and the acceptable safety profile, the benefit risk profile of DepoCyte was considered to be favourable.

Recommendation
Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of DepoCyte in the treatment of intrathecal treatment of lymphomatous meningitis was favourable, and therefore recommended the granting of the marketing authorisation for the indication: "Intrathecal treatment of lymphomatous meningitis. In the majority of patients such treatment will be part of symptomatic palliation of the disease".