European Medicines Agency
Evaluation of Medicines for Human Use

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ASSESSMENT REPORT
FOR
THALIDOMIDE PHARMION

International Nonproprietary Name:
THALIDOMIDE

Procedure No. EMEA/H/C/823

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Pharmion Ltd. submitted on 22 January 2007 an application for Marketing Authorisation to the European Medicines Agency (EMEA) through the centralised procedure for Thalidomide Pharmion, which was designated as an orphan medicinal product EU/3/01/067 on 20 November 2001. Thalidomide Pharmion was designated as an orphan medicinal product in the following indication: treatment of multiple myeloma. The calculated prevalence of this condition was 1.2 per 10 000 EU population.

The applicant applied for the following indication:

Thalidomide Pharmion in combination with melphalan and prednisone for the treatment of patients with untreated multiple myeloma ≥ 65 years or ineligible for high dose chemotherapy.

Thalidomide Pharmion in combination with dexamethasone for induction therapy prior to high dose chemotherapy and bone marrow transplant, for the treatment of patients with untreated multiple myeloma.

Thalidomide Pharmion is prescribed and dispensed through the Pharmion Risk Management Programme (see section 4.4).

Similarity
Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application contained a critical report addressing the possible similarity with authorised orphan medicinal products.

Protocol Assistance
The applicant received Protocol Assistance from the CHMP on 15 June 2005 (for relapsed refractory multiple myeloma). The Protocol Assistance pertained to clinical aspects of the dossier.

Licensing status:
Thalidomide Pharmion 50mg Hard Capsules has been given a Marketing Authorisation in Australia on 7 October 2003, in Israel on 26 August 2004 and 23 April 2007, in New Zealand on 18 December 2003, in Turkey on 31 May 2004, in Thailand on 8 June 2006, in USA on 16 July 1998 and 25 May 2006, in South Africa on 5 October 2007 and in South Korea on 7 April 2006 (orphan approval only).

A new application was filed in the following countries: Hong Kong, Philippines, South Africa.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:
Rapporteur: **Pierre Demolis** Co-Rapporteur: **Tomas P Salmonson**

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 22 January 2007.
- The procedure started on 21 February 2007.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 15 May 2007. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 14 and 15 May 2007. In accordance with Article 6(3) of Regulation (RC) No 726/2004, the Co-Rapporteur declared that he had completed his assessment report in less than 80 days.
- A consultation meeting of Patients' and Victims' organisations (representing their organisations, based on the agreement from the Applicant to disclose relevant confidential data) took place at the EMEA on 30 May 2007 to comment on the Risk Management Plan, the package leaflet and the labelling.

- During the meeting on 18-21 June 2007 the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 21 June 2007 .
- A clarification meeting with the Rapporteurs and the EMEA on the Risk Management Plan took place on 20 June 2007.
- A clarification meeting with the Rapporteurs and the EMEA on the CHMP Day 120 List of Questions took place on 17 July 2007.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 7 September 2007.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 19 October 2007.
- On 5 November 2007, the second consultation of Patients' and Victims' organisations was held to comment on the revised Risk Management Plan, the package leaflet and the labelling.
- During the CHMP meeting on 12-15 November 2007 the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP consolidated list of outstanding issues 21 November 2007.
- The Rapporteurs circulated the updated Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 3 December 2007.
- A clarification teleconference with the Rapporteurs and the EMEA on the CHMP Day 180 list of outstanding issues took place on 4 December 2007.
- During the CHMP meeting on 10-13 December 2007 the CHMP agreed on a second list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP second consolidated list of outstanding issues 18 December 2007.
- The Rapporteurs circulated the updated Joint Assessment Report on the applicant's responses to the second list of outstanding issues to all CHMP members on 11 January 2008.
- Further responses were provided by the applicant on 15 January 2008
- The Rapporteurs circulated the updated Joint Assessment Report on the applicant's further responses to all CHMP members on 18 January 2008.
- The applicant provided final responses on 21 January 2008.
- During the meeting on 21-24 January 2008 the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Thalidomide Pharmion on 24 January 2008. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 22 January 2008
- The CHMP adopted a report on similarity of Thalidomide with Revlimid on19 July 2007.
- The CHMP opinions were forwarded, in all official languages of the European Union, to the European Commission, which adopted the corresponding Decisions on 16 April 2008.

SCIENTIFIC DISCUSSION

1.1. Introduction

Multiple myeloma (MM) is a hematologic cancer in which immature malignant plasma cells (myeloma cells) accumulate in and eventually destroy the bone marrow. The pathological effect of this accumulation is an increasingly dysfunctional bone marrow, causing cytopenias which lead to bacterial infections, anemia, and osteolytic lesions [1-3]. In MM, myeloma cells are monoclonal, producing only one type of immunoglobulin monoclonal protein (M-protein). Normal immunoglobulin production is compromised in myeloma patients, affecting the normal immune response, which predisposes patients to recurrent infections [3]. The light chain of the immunoglobulin accumulates in the kidney, causing renal impairment or failure. The disease accounts for 10% of all haematologic malignancies and 1% of all cancers. Median survival is about 3 years, with infections and renal failure being the most serious, major life-threatening complications [4, 5].

Several national and international guidelines on the management of MM are available in the European Union [6-8], [9, 10]. They recommend that newly diagnosed patients with symptomatic disease should be treated immediately and that treatment should be primarily based on age and performance status. The combination of melphalan with prednisone (MP) was first acknowledged to be superior to melphalan treatment alone in MM by Alexanian *et al* nearly 40 years ago [11] and currently remains standard therapy in Europe for patients aged ≥ 65 years, who are not candidates for high-dose therapy prior to autologous stem cell transplantation (HDT/ASCT) [6-8, 12] [9, 10]. Response rates in this elderly population have been consistently in the range of 50% to 60%, with an overall survival (OS) time of approximately 36 months. Newly diagnosed patients who are eligible for HDT/ASCT (aged < 65 years) are first treated with an induction regimen that can produce a rapid reduction in tumor burden without jeopardizing stem cell mobilization and collection [7, 8, 10, 13]. There is no standard regimen for induction of remission in Europe. However, VAD (vincristine, doxorubicin, dexamethasone) or VAD-like induction regimens have been widely used and are recommend in several country guidelines [6-8] [9, 10, 13]. VAD and VAD-like regimens are associated with complete response (CR) rates ranging from 10% to 25% [7]. The responses and remissions observed with these regimens, however, are generally of short duration. When used as primary therapy, no overall survival advantage compared with MP has been shown [9, 10]. Studies have demonstrated highly similar antimyeloma efficacy for VAD and dexamethasone in newly diagnosed patients as primary therapy and induction therapy [14, 15]. However, current guidance documents do not consider dexamethasone alone as a standard for induction [16]. A high-dose, single-agent pulsed regimen of this agent is recommended in Europe as monotherapy for induction of remission in newly diagnosed patients proceeding to transplant and in need of a rapid response because of severe pancytopenia, impaired renal function, or spinal cord compression [7-9].

Despite progress in its current treatment and management, MM remains incurable. Although HDT/ASCT has extended survival in newly diagnosed myeloma [17], all patients eventually relapse and a plateau is never observed on EFS curves [17, 18]. Newer agents such as thalidomide, lenalidomide and bortezomib are being combined with standard MM therapies for newly diagnosed patients in an attempt to enhance responses and improve outcomes. Lenalidomide and bortezomib are authorized for treatment in the relapsed setting [19]. The use of thalidomide in combination with MP has recently become a recommended standard therapy based on the data provided in this submission [20, 21].

1.2. Quality aspects

Introduction

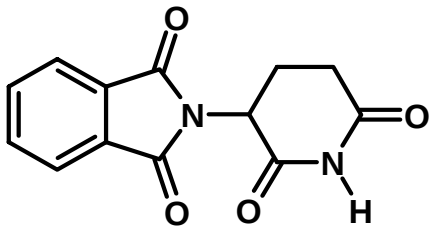
Thalidomide Pharmion is presented as opaque, white, hard gelatin capsules containing 50 mg of thalidomide (active substance). The excipients used in the preparation of Thalidomide Pharmion are well known excipients used in hard capsules preparations such as anhydrous lactose, microcrystalline cellulose, crospovidone, povidone, stearic acid, colloidal anhydrous silica (capsule content), gelatin

and titanium dioxide (capsule shells) shellac, black iron oxide and propylene glycol (black printing ink).

Thalidomide Pharmion 50 mg hard capsules are marked in black ink with "Thalidomide 50 mg Pharmion". The capsules are packaged in PVC/PE/Aclar/aluminium blisters and the blisters are sealed in a paperboard wallet card.

Active Substance

The active substance is chemically designated as 2-(2,6-dioxo-3-piperidyl)isoindole-1,3-dione (IUPAC) or 1H-isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (CAS) and has the following structure:



It is a white to off-white powder, which melts in the range 267 – 273 °C. The octanol/water partition coefficient at room temperature is 5. Thalidomide is classified as "very slightly soluble" in water (1000 to 10 000 ml per gram).

Thalidomide may exist in two polymorphic forms α and β however the commercially utilised manufacturing process leads only to the α form.

Thalidomide contains single asymmetric carbon atom alpha to the phthalimido nitrogen. The molecule can, therefore, exist in a two complimentary optically active forms. The drug substance developed is a racemic mixture that contains an equal amount of the S(-) and R(+) forms, and therefore has a net optical rotation of zero. The use of a racemic mixture is justified by the fact that each of the optically active forms undergoes rapid racemisation in vivo under normal conditions.

- Manufacture

The manufacturing process is a four-step synthesis process comprising two chemical reaction steps which are followed by purification and milling. During the synthesis one intermediate product is isolated. The proposed manufacturing process has been well described, critical steps and accompanying in-process controls have been identified. Appropriate specifications for the starting materials, intermediate and reagents have been established.

There have been no significant changes to the drug substance manufacturing process during the development of drug substance. Manufacturing process development investigations have been performed at small scale to identify the reaction parameters which could impact the yield and purity of the intermediate and the drug substance. Obtained results have led to the selected drug substance manufacturing conditions.

Key physicochemical properties of the drug substance that can influence the drug product and its manufacture, including solubility, dissociation constants, choice of racemate, polymorphism and particle size have been discussed and justified.

The chemical structure of the drug substance has been confirmed by FT-IR spectroscopy, ^{1}H and ^{13}C NMR spectroscopy, UV spectroscopy, melting point and elemental analysis. The elemental analysis data of C, H, N and O of the thalidomide study batch correspond with the theoretical values and with the results obtained on the reference substance. The IR, ^{1}H NMR, ^{13}C NMR, and UV spectra of the in-house substance and the reference substance are also consistent with each other and with the known structure of thalidomide.

The assessment of possible polymorphism has been performed using X-ray powder diffraction. The proposed manufacturing process allows to control the final polymorphic form through solvent selection and re-crystallization conditions to consistently produce the α-form. In addition it has also been shown in a bioequivalence study, in which the α and β polymorphs were administrated to healthy subjects, that the two polymorphs are bioequivalent with respect to C_{max}, AUC(0-t) and AUC(0-inf).

- Specification

The drug substance specification is in line with the USP monograph for thalidomide with additional tests for residual solvents and particle size. The proposed specification includes tests for appearance, identification (FT-IR and HPLC), assay (HPLC), impurities (TLC and HPLC), residual solvents (GC), heavy metals, water content (Karl Fisher), particle size (Laser light scattering) and bioburden.

The drug substance is tested against the USP monograph for thalidomide (as the Thalidomide Monograph is not included in the Ph. Eur.).

For the particle size method, instrument performance is verified with glass microspheres on a routine basis.

The GC method has been validated for selectivity, linearity, limit of quantitation (LOQ), limit of detection (LOD), system precision, range and accuracy. The robustness of the method has also been checked and confirmed.

In general, analytical methods proposed are suitable to control the quality of the drug substance.

Batch analysis data have been provided for all batches of the drug substance used in the non-clinical and clinical studies as well as for three commercial scale batches manufactured at the proposed manufacturing site. All batches complied with the requirements from the drug substance specification.

- Stability

Stability studies have been performed on seven commercial scale batches of the drug substance. Data was provided for batches stored up to 36 months at 25 °C/60 % RH (long term stability studies) and 6 months at 40 °C/75 % RH (accelerated conditions). Additionally, data from photostability study (conditions according to ICH Q1B, Option 2) and from the stressed degradation studies (thermal degradation, oxidative, acidic and alkaline degradation).

The data provided show that thalidomide is very stable in the solid state and that it is prone to hydrolysis in aqueous solution, especially in an alkaline pH.

The stability data provided for the drug substance confirmed the proposed re-test period.

Medicinal Product

- Pharmaceutical Development

In early clinical development a simpler clinical formulation (consisting of a bulking agent and lubricant) than the commercial formulation was used. During commercial scale development, conventional components were used to facilitate the scale-up during manufacture.

The commercial manufacturing process is the same process utilized to prepare drug product throughout clinical development. The manufacturing process has consistently utilized the same drug substance from the same supplier and the same compendial excipients through development. All drug product manufacturing operations have been performed at the same site utilizing equipment with the same operating principles at the same process scale throughout development.

The proposed *in vitro* dissolution method is the one described in USP monograph for Thalidomide Capsules.

- Adventitious Agents

Among excipients used in the drug product only lactose (ingredient of the formulation) and gelatin (component of the capsule shell) are of animal origin. Declarations from the lactose suppliers were provided, stating that the lactose was sourced from healthy animals under the same conditions as milk collected for human consumption.

For gelatin used for manufacture of capsule shells a PhEur TSE Certificates of Suitability were provided.

Stearic acid used in the formulation is of vegetable origin.

- Manufacture of the Product

The commercial manufacturing process of the drug product, which utilizes conventional solid dosage form manufacturing procedures and equipment, can be summarized as dry ingredient blending followed by roller compaction and encapsulation. Blending ensures homogeneity of the thalidomide and excipients, while roller compaction is employed to ensure consistent flow characteristics of the granulated powder blend during encapsulation.

The critical steps of the manufacturing process have been identified and adequately studied. Appropriate in-process controls of the critical steps have been established.

The manufacturing process has not changed throughout the development. More than 50 batches of the drug product have been manufactured at the proposed scale using the same process. Process validation was carried out on three batches of commercial scale and showed that the capsules can be manufactured reproducibly according to the finished product specifications.

- Product Specification

The USP monograph for thalidomide capsules was used as a guideline for setting specifications for the drug product. The proposed specifications include tests for appearance, identity (HPLC and TLC), assay (HPLC), uniformity of dosage units (HPLC), impurities (HPLC), dissolution and bioburden.

All methods have been satisfactorily validated. The HPLC method for an assay was validated with regards to specificity, linearity, accuracy, precision and robustness. The method for the related substances was validated for specificity, linearity, accuracy, precision, limit of detection, limit of quantification and robustness. The test conditions for the dissolution method are taken from the USP monograph for thalidomide capsules. The method was validated for specificity, linearity, accuracy, precision, solution stability and effect of filtration of the sample.

Batch analysis data on three commercial scale and one of pilot scale batches of the drug product confirmed consistency of the manufacturing process. All results comply with specifications.

The packaging for Thalidomide Pharmion is presented as wallet design where the blister strips are sealed into a wallet card. The blister strips are integral to the package and are not intended to be separated from the package. The applicant has committed to perform further development work on the product package.

- Stability of the Product

Complete long term (25 °C/60 % RH) and accelerated (40 °C/75 % RH) stability data have been provided for ten batches of the drug product, nine of which were of commercial scale. In addition five commercial scale batches have been placed on long term stability studies and for these batches up to 12 - 36 months results were reported. All results remain within the specifications and prove that the drug product is stable. A photostability study has showed that the drug product is not light sensitive.

The applicant has committed to place at least one commercial batch of drug product in the stability program each year, according to the approved stability protocol.

In summary the stability data provided support the proposed shelf-life and storage conditions as defined in SPC.

Discussion on chemical, pharmaceutical and biological aspects

The drug substance and the drug product have been appropriately described and generally satisfactory documentation has been provided. The excipients used in the preparation of the drug product and manufacturing process selected are standard for capsules preparation. The results indicate that the drug substance and the drug product can be reproducibly manufactured.

At the time of the CHMP opinion, there was minor unresolved quality issue which have no impact on the Benefit/Risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve it as a Follow-up Measure after the opinion, within an agreed time-frame.

1.3. Non-clinical aspects

Introduction

The pivotal non-clinical studies were conducted according to Good Laboratory Practice (GLP) standards, as claimed by the applicant. Studies from the published literature were not conducted according to GLP. Study data obtained from the Office of Freedom of Information were derived from studies which were not conducted according to GLP.

Pharmacology

- Primary pharmacodynamics

No studies on primary pharmacology have been performed by the applicant. Reference was made to published data. The primary pharmacological actions of thalidomide described in the literature include anti-angiogenic and immunomodulatory/anti-inflammatory activity. The mechanisms involved in these activities of thalidomide have not been fully delineated. However, it is likely that common mechanisms may be involved in both the anti-angiogenic and immunomodulatory/anti-inflammatory effects.

Proposed mechanisms for the anti-angiogenic activity of thalidomide include (1) a down-regulation of TNF-α levels; (2) down-regulation of Vascular Endothelial Growth Factor (VEGF) expression; (3) inhibition of the response to basic Fibroblast Growth Factor (bFGF) and VEGF potentially through the modulation of integrin expression and impairment of migration; (4) inhibition of endothelial cell proliferation; and (5) blocking of cyclooxigenase-2 (COX-2) induction. Thalidomide has also been shown to be efficacious in several animal models of immune-mediated and pain induced inflammatory disorders and TNF-α-induced conditions, and to induce apoptosis in human peripheral blood monocytes. More recent studies have implicated the inhibition of Nuclear Factor-κB (NF-κB) activity in the extensive series of biological activities associated with thalidomide.

In multiple myeloma (MM), thalidomide has been shown to induce apoptosis or growth arrest in the G1 phase of the cell cycle in several MM cell lines and in patient derived MM cells resistant to melphalan, doxorubicin and dexamethasone. Thalidomide was also shown to enhance the anti-MM activity of dexamethasone in MM cell lines. In animal models of MM thalidomide has demonstrated some evidence of anti-angiogenic activity, as well as directly inhibiting myeloma growth.

The efficacy of thalidomide in combination with a number of chemotherapeutics has been demonstrated in a variety of animal models of human cancers. These include combinations with dimethylxantheone and paclitaxel in colorectal adenocarcinomas; decarbazine in melanoma; recombinant diabody in B-cell lymphoma; paclitaxel in hepatocellular carcinoma; carmustine, cisplatin, BCNU and temozolomide in glioma; and cyclophosphamide in prostate cancer.

- Secondary pharmacodynamics

The main secondary pharmacodynamic activity of thalidomide (investigated in mouse, rats and cats intravenously and *per os*, up to 1000 mg/kg) concerns its CNS activity. As thalidomide was initially approved as a sedative in Europe, the CNS properties of this product are well known (see also non-clinical safety pharmacology section).

- Safety pharmacology programme

Cardiovascular effects

The effect of thalidomide on hERG tail current recorded from HEK293 cells stably transfected with hERG cDNA showed an inhibition of less than 25% at the limit of thalidomide solubility at 75 µg/ml. In dog isolated Purkinje fibres there was a reduction in action potential duration at ≥12.5 µg/ml, and at 125 µg/ml there was a reduction in maximum rate of depolarization. In the company-sponsored 1-year oral dosing study in dogs, thalidomide-related electrocardiographic alterations were not observed at doses up to 1000 mg/kg/day.

CNS effects

Thalidomide was initially approved as a sedative in Europe. Thalidomide has been shown to increase slow wave sleep with little or no change to percent rapid eye movement (REM) sleep, and to decrease sleep onset latency in rats and cats. In addition, it has been shown to modulate a number of measures of neurological function in rats and mice that include a decrease in spontaneous motor activity, an increase in protection in electroshock-induced seizures, and potentiation of chlorpromazine- and reserpine-induced catalepsy and morphine analgesia. Data suggest that the activity of thalidomide may, in part, be related to a thalidomide-induced decrease in utilization/release of serotonin.

In the company-sponsored repeat-dose toxicity studies, potential CNS depression was only noted during a thorough functional observation battery evaluation where partially or completely closed eyelids were observed in rats after 90 days treatment at an oral dose of 3000 mg/kg/day.

- Pharmacodynamic drug interactions

Thalidomide has been shown to enhance the sedative effect of barbiturates, ethanol, chlorpromazine, and reserpine.

Pharmacokinetics

Single dose pharmacokinetic and bioavailability studies were conducted in mice and rats (oral and intravenous routes). The metabolism of thalidomide was studied *in vitro* with human microsomal preparations and in mouse plasma. Reference to data from the literature was also provided.

A high performance liquid chromatographic assay was validated for determination of thalidomide concentrations in mouse, rat and dog plasma. High performance liquid chromatography-mass spectrometry (HPLC/MS/MS) analysis method was used to determine the level of thalidomide in rabbit semen and to determine the level of thalidomide in rabbit milk and heparinized plasma samples.

- Absorption

Male mice (6/group/timepoint) received thalidomide as a single intravenous dose (PEG-400 solution) of 10 mg/kg or a single oral dose (1% CMC suspension) of 200, 1000, or 2000 mg/kg. Male rats (3/group/timepoint) received thalidomide as a single intravenous dose (PEG-400 solution) of 5 mg/kg or a single oral dose (1% CMC suspension) of 100, 500, and 1000 mg/kg (see table 1).

Table 1: Thalidomide pharmacokinetics parameters in male mice and rats following a single oral or intravenous dose of thalidomide.

Species	Mouse				Rat			
Route of administration	Oral			IV	Oral			IV
Dose (mg/kg)	200	1000	2000	10	100	500	1000	5
Cmax (µg/ml)	22.7	30.7	29.0	5.13	21.6	34.4	29.9	6.79
Tmax (hr)	0.5	1	4	0.083	6	12	6	0.083
AUC0-48 (µg·hr/ml)	103	315	315	2.12	348.5	1063	882.9	17.84
T1/2e	3	12	7.6	0.38	3.5	4.3	4.6	2.0
Abs. bioavail.	2.4	1.5	0.74	1.0	0.98	0.60	0.25	1.00

- Distribution

Plasma protein binding data for thalidomide are not available in animals. Plasma protein binding in humans is 55% and 66% for the R(+) and S(-)enantiomers, respectively. In the rhesus monkey, thalidomide was rapidly distributed into tissues. Ten minutes following intravenous administration of ^{3}H -thalidomide at 10 mg/kg, the highest percentage of total radioactivity was found in the liver (18.9%, of which 46.5% was unchanged thalidomide). Total radioactivity in the plasma, muscle and brain ranged from 6.8% to 8.8%, primarily unchanged thalidomide (80.9% to 90.2%).

In pregnant mice autoradiography of sagittal sections from whole animals showed the presence of a large amount of thalidomide-derived radiolabel confined to the gastrointestinal tract. Slightly higher concentrations were observed for the liver and kidney; otherwise, the distribution of thalidomide was uniform with placental and fetal tissues showing about the same concentration as maternal tissues.

As part of the developmental and perinatal/postnatal reproductive toxicity study in rabbits, including a postnatal reproductive evaluation (segment III), a subgroup of animals was administered thalidomide in the same manner as the main study animals. During study preweaning weeks 1, 2, 3, and 4 blood samples from the auricular artery and milk samples were collected from the 5 female rabbits/subgroup at approximately 3 hours (approximately at C_{max}) following treatment (see table 2).

Table 2: Mean milk and plasma thalidomide levels

		Preweaning Week 1		Preweaning Week 2		Preweaning Week 3		Preweaning Week 4	
group	Dose mg/kg/day	Milk (ng/ml)	Plasma (ng/ml)	Milk (ng/ml)	Plasma (ng/ml)	Milk (ng/ml)	Plasma (ng/ml)	Milk (ng/ml)	Plasma (ng/ml)
I	0 (vehicle)	84	NS	61	NS	13	NS	44	NS
II	30	13435	10175	15733	9798	8178	3876	7742	6648
III	150	32940	18506	35625	20562	22200	21200	36075	14815
IV	500	49120	21648	62800	17300	15748	24608	71425	25750

NS = No sample

As part of the fertility and general reproductive toxicity study of thalidomide in rabbits (segment I), semen samples from each male rabbit approximately 1 hour post dose (at least 22 males/group) were collected after at least 56 days of dosing (see table 3).

Table 3: Mean semen thalidomide concentrations

Dose mg/kg/d	0 (vehicle)	30	150	500
Concentration (ng/ml)	1362 ± 3864	2673 ± 1233	9136 ± 3416	15401 ± 5643

- Metabolism

***In vitro* metabolism of thalidomide by microsomal preparations**

Thalidomide (10µg/ml) was incubated with pooled human hepatic microsomes and microsomes isolated from human B lymphoblastoid cell lines that had been transfected with specific isozymes of P450 (cloned microsomes). Cloned microsomes included CYP 1A2, CYP 2A6, CYP 2B6, CYP 2C9, CYP 2C19, CYP 2D6, CYP 2E1 and CYP 3A4. Microsomes and S9 preparations from aroclor- or Phenobarbital-induced rat liver were also incubated with thalidomide. The incubations were extracted and analysed by HPLC for the potential hydroxylated thalidomide metabolites, N-hydroxythalidomide (N-OH-Thal), 3-hydroxythalidomide (3-OH-Thal) and 4-hydroxythalidomide (4-OH-Thal).

Thalidomide was not oxidized to any of these metabolites by any of the cloned microsomes and was poorly oxidized by pooled-human microsomes or rat hepatic microsomes or S9. Low amounts of HPLC peaks comigrating with 4-OH-Thal, 3-OH-Thal and an unknown metabolite with a lower retention time than the three potential hydroxylated metabolites were observed. Thalidomide at a concentration of 10µg/ml did not inhibit oxidation of known substrates of each of the P450 isozymes tested in either cloned microsomes or pooled human microsomes.

Analysis of thalidomide and Metabolites in Mouse Plasma

Three CD-1 mice were dosed orally with 3000 mg/kg thalidomide in 1% carboxymethylcellulose daily for three days and plasma samples were obtained 2, 4 and 6 hours postdose on the third day. Extracts of mouse plasma from thalidomide treated mice contained at least four components that absorbed at 230nm, not observed in control plasma extracts. The first two components did not match any standards and may represent other metabolites, possibly hydrolysis products of thalidomide. The second pair of components closely matched standards for 4-hydroxythhalidomide and thalidomide respectively.

In rats, rabbits, dogs, mice, and guinea pigs urine, the most abundant products were α-(o-carboxybenzamido)glutarimide, 4-phthalimidoglutaramic acid, and 2-phthalimidoglutaramic acid which are hydrolysis products. Additional human studies have shown that thalidomide does not affect its own metabolism, nor does it affect the metabolism of oral contraceptive hormones. Thus, clinically

important interactions between thalidomide and drugs that are metabolised by the CYP enzyme system are unlikely.

- Excretion

No studies evaluating the excretion of thalidomide have been performed by the applicant. Based on data from the literature, following administration of radio labelled thalidomide in different species (rat, rabbit, monkey), radioactivity is mainly excreted in urine. At least 90% of the radioactive urinary material was excreted within 24 hours. However, with the largest oral doses, urinary excretion was progressively delayed, because of the rate of absorption which is decreased.

- Pharmacokinetic drug interactions

No studies have been conducted to evaluate pharmacokinetic drug interactions with thalidomide.

Toxicology

Table 4: Overview of GLP compliant toxicology studies conducted with thalidomide

	route	duration	dose levels (mg/kg)
Repeat-Dose Toxicity			
Mouse / CD-1	Oral (gavage)	14 days	0, 50, 200, 750, 3000
Mouse / CD-1	Oral (gavage)	13 weeks	0, 30, 300, 3000
Rat / Fischer	Oral (gavage)	14 days	50, 200, 750, 3000
Rat / Fischer	Oral (gavage)	13 weeks	0, 30, 300, 3000
Dog / Beagle	Oral (capsule)	28 days	0, 12, 100, 1000, 2000
Dog / Beagle	Oral (capsule)	53 weeks	0, 43, 200, 1000
Genotoxicity			
Reverse mutation	*In vitro*	NA	50, 167, 500, 1670, 5000, 10000 µg/plate in DMSO
XPRT Forward Gene Mutation	*In vitro*	NA	0.0167, 0.05, 0.167, 0.5, 1, 1.67, 2.5, 5, 10, 16.7, 25, 50, 100, 167, 250, 500, 1000 µg/ml in DMSO
Mouse / CD-1 Micronucleus	Intraperitoneal	NA	0, 500, 2500, 5000
Carcinogenicity			
Mouse / CD1	Oral Gavage	At least 104 weeks	0, 100, 1000, or 3000 mg/kg/day
Rat / Fischer 344 (F344/NHsd)	Oral Gavage	At least 104 weeks	0, 20, 160, or 300 mg/kg/day to males 0, 30, 300, or 3000 mg/kg/day to females
Reproductive and Developmental Toxicity			
Fertility — Rabbit / New Zealand White	Oral (Stomach tube)	14 days prior to mating up to and including gestation day 7 (DG7)	Group 1 females - and males 0, 10, 50 and 100 mg/kg/day Group 2 females – no treatment Males - 0, 30, 150, 500 mg/kg/day
Peri and Postnatal — Rabbit / New Zealand White	Oral (stomach tube)	DG 18 through DL 28 for rabbits that delivered a litter or DG 33 for rabbits that did not deliver a litter	0, 30, 150 and 500 mg/kg/day

- Single dose toxicity

No acute toxicity study has been performed by the applicant. Data taken from the literature show that the acute toxicity of thalidomide has been investigated in mice, rats, guinea pigs, dogs and monkeys and indicate that acute toxicity of thalidomide is quite low. The R(+) and S(-) forms were more toxic than the (±) optical form, with oral LD50s of 0.4 and 0.7 g/kg, for the R(+) and S(-) forms, respectively. However, the relevance of this finding is questionable considering the rapid interconversion between the two forms that occurs *in vivo*. In humans, no mortality from overdoses or attempted suicide has been recorded so far, even at doses of up to 14,000 mg. CNS effects such as drowsiness and somnolence may be expected events in a proportion of patients receiving this drug based on the well-known sedative properties of thalidomide.

- Repeat dose toxicity (with toxicokinetics)

Repeat dose GLP toxicity studies were conducted in mice, rats and dogs (see table 4: above).

Clinical observations in these studies were:

- Discoloured urine in mice (pink to red) (≥ 30 mg/kg/day) and dogs (green) (≥ 12 mg/kg/day);
- White material (unabsorbed thalidomide) in faeces of dogs (≥ 43 mg/kg/day);
- Enlarged and/or blue discoloration of mammary glands (≥ 43 mg/kg/day) and prolonged oestrus (1000 mg/kg/day) in female dogs; and
- Decreased body weight and food consumption in rats (≥ 30 mg/kg/day).

Clinical pathology parameters in the repeat-dose studies revealed:

- Decreased platelet counts in the two-week mouse (50 and 3000 mg/kg/day) and in the two-week (≥ 200 mg/kg/day) and 13-week (≥ 30 mg/kg/day) rat studies;
- Decreased protein, and albumin in the two-week rat study (3000 mg/kg/day); and
- Decreased glucose values (≥ 12 mg/kg/day) in one-month dog study.

Pathology findings in the repeat-dose studies were:

- Increased liver weights with centrilobular hepatocellular hypertrophy in the two-week (≥ 200 mg/kg/day) and 13-week (≥ 300 mg/kg/day) mouse studies;
- Decreased thymic weight with no corollary microscopic changes in the 13-week rat study (300 and 3000 mg/kg/day); and
- Discoloured (yellow/green) bones (≥43 mg/kg/day) with no corollary microscopic changes, mammary gland dilatation (ducts) and glandular epithelium hyperplasia (females only) (≥ 43 mg/kg/day), and bile plugs in canaliculi (males only) (1000 mg/kg/day) in the one-year dog study.

- **Toxicokinetics**

Repeat-dose toxicity studies in rats and dogs did not show any important safety concerns. One of the most important clinical safety concerns, peripheral neuropathy, has not been observed in the non-clinical toxicity studies. It appears that the animal models (see table 5) are poorly predictive for thalidomide toxicity in humans.

Table 5: Thalidomide toxicokinetic data in mice, rats and dogs

Time Period	Species / Sex	Dose (mg/kg/day)	Mean		Animal:Human AUC ratio at human dose
			Cmax (µg/mL)	AUC 0-∞ (µg·hr/mL)	200 mg[a]
Day 8	CD-1 mice / male	50	3.32	5.61	0.3
		200	9.54	43.64	2.4
		750	15.91	112.71	6.3
		3000	27.67	179.68	10.0
	CD-1 mice / female	50	3.79	7.85	0.4
		200	10.07	41.09	2.3
		750	15.29	80.67	4.5
		3000	28.18	191.97	10.7
Day 90	CD-1 mice / male	30	2.56	25.15	1.4
		300	14.18	92.79	5.2
		3000	27.72	253.34	14.1
	CD-1 mice / female	30	3.97	59.27	3.3
		300	10.36	84.78	4.7
		3000	16.00	175.02	9.7
Day 8	Fischer rats / male	50	4.57	43.79	2.4
		200	6.53	87.94	4.9
		750	13.73	210.06	11.7
		3000	15.47	372.02	20.7
	Fischer rats / female	50	4.87	55.25	3.1
		200	6.83	96.53	5.4
		750	17.23	292.48	16.2
		3000	20.45	505.77	28.1
Day 90	Fischer rats / male	30	7.68	NA	NA
		300	14.98	298.99	16.6
		3000	19.84	1153.70	64.1
	Fischer rats / female	30	10.78	91.11	5.1
		300	20.56	387.36	21.5
		3000	36.00	645.96	35.9
Day 364	Beagle dogs / male	43	2.77	19.48	1.1
		200	3.53	34.68	1.9
		1000	9.47	222.56	12.4
	Beagle dogs / female	43	2.07	32.30	1.8
		200	4.36	64.71	3.6
		1000	9.03	323.81	18.0

a) Human AUC = 18 µg·hr/ml at 200 mg dose

- Genotoxicity

Table 6: Genotoxicity studies (GLP) conducted for thalidomide

Type of test/study	Test system	Concentrations/ Metabolising system	Results
Gene mutations in bacteria	S. typhimurium TA1535; 1537; 98; 100; 102; E. coli WP2 uvrA	up to10000 µg/plate (+/- S9)	negative
Gene mutations in mammalian cells	CHO-cells, XPRT locus	up to 1000 µg/ml (+/- S9)	negative
Chromosomal aberrations *in vivo*	Mouse, micronuclei in bone marrow	500; 2500; 5000 mg/kg	negative

In the Ames/Salmonella-E. coli reverse mutation assay Thalidomide did not alter the background bacterial lawn to Salmonella and E. coli bacterial strains over the range of concentrations tested (50 – 10,000 µg/plate). At ≥5000 mg/plate, thalidomide precipitated from solution; however, it was not toxic to the tester strains even under these conditions. Thus, the precipitation did not adversely impact the interpretation or results of this assay. Revertant frequencies for all concentrations of thalidomide in all tester strains with metabolic activation, and in all Salmonella strains without metabolic activation, under plate incorporation conditions, approximated or were less than those observed in the concurrent negative controls. Statistically significant increases in revertant frequencies were observed using the E. coli strain without metabolic activation under plate incorporation conditions.

Thalidomide was re-evaluated under identical conditions in strain WP2 *uvr*A without S9 using plate incorporation conditions, and in strain TA1537 with S9 using liquid pre-incubation conditions to

verify the observed slight increases in revertant frequency. Under these repeated conditions, increases above control levels were not observed. Thus, the slight increases observed in the original assays are considered to be statistical aberrations due to random fluctuation of the spontaneous revertant frequencies.

Thalidomide was evaluated in a AS52/XPRT Mammalian Cell Forward Gene Mutation Assay to determine its ability to induce mutations at the xanthine-guanine phosphoribosyl transferase (XPRT) locus in cultured AS52 Chinese hamster ovary (CHO) cells. In duplicate cultures in an initial and a confirmatory assay, with S9 and without S9, there were no statistically significant or dose-dependent increases in the average mutation frequencies of the cultures treated with thalidomide. In an independent confirmatory assay a statistically significant increase in average mutant frequency was observed at a concentration of 5.00 µg/ml without S9. However, this increase was not linear, and it did not represent a two-fold net increase relative to the pooled concurrent negative controls. Thus, this isolated increase did not even meet the criteria for an equivocal response. The slight increase in mutant frequency observed at a single concentration without S9 in the confirmatory assay is considered to be a statistically aberration due to random fluctuation of the spontaneous mutant frequency. All positive and negative controls were within acceptable ranges.

In the *in vivo m*icronucleus test with thalidomide in mouse bone marrow erythropoietic cells, no clinical signs of toxicity were observed at 500 mg/kg. Decreased activity and writhing were noted immediately after dosing ≥2500 mg/kg thalidomide and persisted up to 24 hours post-dose in a few animals of the 5000 mg/kg dose group. Bone marrow from the femurs of mice receiving 0 - 5000 mg/kg of thalidomide intraperitoneally and sacrificed at 24, 48, or 72 hours after dosing, were scored for the number of micronucleated polychromatic erythrocytes (MPECs). Positive control mice were sacrificed 24 hours after intraperitoneal injection. Analysis of the data indicated that thalidomide did not induce any statistically significant or dose-dependent increases in MPCE frequencies at any dose or sacrifice time as compared to negative controls. The PCE:NCE ratios were depressed at the 24-hour time point in mice receiving ≥2500 mg/kg providing evidence of bone marrow exposure to the test article.

- Carcinogenicity

Table 7: Oral carcinogenicity studies in mouse and rat.

Species	**Dose (mg/kg/day)**	**Exposure (AUC)**	**Major findings**
Mouse GLP[1]	0, 0, 100, 1000, 3000 (N=60)	3000 mg/kg: 268 µg·hr/ml (males)	No carcinogenicity. No effects on survival, clinical signs or ophthalmologic parameters. Increase in body weight in females at all doses, increased Hb in males at ≥1000 mg/kg, increased absolute and relative liver weights with hepatocyte hypertrophy at ≥100 mg/kg in males and ≥1000 mg/kg in females.
Rat GLP	Male: 0, 0, 20, 160, 300 Female: 0, 0, 30, 300, 3000 (N=50)	300 mg/kg: 227 µg·hr/ml (males) 3000 mg/kg: 692 µg·hr/ml (females)	No carcinogenicity. Dose-related decreases in survival, body weights, body weight gains, and food consumption. Increased incidence of pancreatic islets metaplasia, characterised by the presence of cells with morphologic appearance of hepatocytes around pancreatic islets.

1) Analytical chemistry analysis was not performed according to GLP standards

A subgroup of male mice (21 males/group) in groups 3, 4, and 5 (100, 1000, and 3000 mg/kg/day respectively) was administered (±)thalidomide by oral gavage in the same manner as the main study animals. On study Day 7, blood samples were collected under carbon dioxide/oxygen anaesthesia via puncture of the orbital venous sinus from 3 males/group/time point at 0 (pre-dose), 0.5, 1, 2, 6, 12, 18, and 24 hours following treatment. Additionally, single blood samples were also taken at the terminal sacrifice during Week 105 from selected animals from the main study groups. These samples were collected approximately 24 hours after the final dose.

Table 8: Thalidomide toxicokinetics in mice from an oral gavage 104-week carcinogenicity study

	Study Day 7			Study Week 105					
	Male	Male	Male	Male	Female	Male	Female	Male	Female
Dose (mg/kg/day)	100	1000	3000	100	100	1000	1000	3000	3000

AUC_{0-24} (ng·hr/mL)	21304	113994	268050	ND	ND	ND	ND	ND	ND
C_{max} (ng/mL)	3935	16233	23575	ND	ND	ND	ND	ND	ND
C_{min} (ng/mL)	123	47	300	<20	81	182	299	4833	4358
T_{max} (h)	2.0	2.0	1.0	ND	ND	ND	ND	ND	ND
$T_{1/2e}$ (h)	5.89	2.47	3.09	ND	ND	ND	ND	ND	ND

ND=Not determined

Table 9: Animal:Human ratios

Time Period	Species / Sex	Dose (mg/kg/day)	Mean		Animal:Human AUC Ratio at Human Dose
			Cmax (µg/ml)	AUC 0-24 (µg·hr/ml)	200 mg[a,b]
Day 7	CD-1 mice / male	100	3.9	21.3	1.2
		1000	16.2	114.0	6.3
		3000	23.6	268.0	14.9

a = Proposed human starting dose and median dose administered in pivotal Phase III study; b = AUC 0-t of 18 µg•hr/ml used for calculations (see Clinical Summary

- Reproduction Toxicity

Reproductive and developmental toxicity

Table 10: Overview of reproductive and developmental toxicity studies

Study	Species number/ group	Route & dose	Dosing period	Major findings	NOAEL
Fertility GLP compliant	NZW rabbits 25/sex/group	0 M:30/F:10 M:150/F:50 M:500/F:100 mg/kg oral (stomach tube)	M: 14 days prior to mating to day of sacrifice (56 total days of dose administration) F: 14 days prior to mating through day 7 of gestation	- Degeneration of the germinal epithelium of the testicles - Increase in resorbed conceptuses in treated females - Decrease in Fertility Indice F0: Abortion	Fertility: M: 500 mg/kg F: 10 mg/kg
Peri / post natality GLP compliant	NZW rabbits 25/group	0 30 150 500 mg/kg oral (stomach tube)	On Day 18 of gestation through Day 28 of lactation/postpartum (did deliver a litter) or Day 33 (did not deliver a litter)	F1: Splayed limbs, minimal neuropathy, decrease in body weight gain, decrease in pregnancy indice	F0: LOAEL = 30 mg/kg F1: 30 mg/kg

Abbreviations: F: Female; M: Male

Fertility and early embryonic development

One oral fertility and general reproduction toxicity study (Segment I – ICH Harmonised Tripartite Guidelines stages A through D of the reproductive process) has been conducted in rabbits. Female rabbits were randomly assigned to four dosage groups (0, 10, 50 and 100 mg/kg/day) of 25 rabbits per group and were dosed from 14 days prior to mating up to and including gestation day 7 (DG7). The four groups of males (25 per group) were dosed with 0, 30, 150, or 500 mg/kg/day from 14 days prior to mating with a second set of 100 untreated females. Dosing of the males continued through mating until the day before sacrifice – a minimum of 56 days.

The no observable adverse effect level (NOAEL) for maternal toxicity was less than 10 mg/kg/day and the paternal NOAEL was less than 30 mg/kg/day. Body weights were adversely affected by dosages of 10 mg/kg/day in females and 30 mg/kg/day in males.

The NOAEL for fertility and reproduction in male rabbits was 500 mg/kg/day (highest dose tested). Sperm motility, count and density were not affected by doses as high as 500 mg/kg/day and semen drug levels demonstrated a dose dependent pattern. Thalidomide caused microscopically evident degeneration of the germinal epithelium of the testicles at a greater incidence in treated rabbits than seen in control rabbits. These changes included multinucleated giant cells in the lumen of the seminiferous tubule and a variable loss of round and elongating spermatids from the seminiferous tubules. These effects were seen in the 30 mg/kg/day group and progressed in incidence and severity through the 150 mg/kg/day and 500 mg/kg/day groups.

Mating and fertility parameters were unaffected by dosages of (±) Thalidomide as high as 100 mg/kg/day. Mating was confirmed in 23, 21, 21 and 23 respective pairings for the four respective dosage group females. There were 24, 21, 17 and 21 pregnant does in the four respective dosage groups resulting in Fertility Indices (number of pregnancies per number of rabbits that mated) of 96.0%, 95.4%, 81.0% and 87.5% in the four respective dosage groups.

The NOAEL with respect to embryonic development for treated male rabbits mated to untreated females was 500 mg/kg/day. Reproductive and litter parameters were comparable amongst the four groups of untreated females.

The NOAEL with respect to embryonic development for treated female rabbits mated to untreated males was less than 10 mg/kg/day. Observations included a decrease in litter averages for corpora lutea, implantations, litter sizes, does with viable fetuses and live fetuses. The number of early resorptions, does with any resorptions, does with all conceptuses resorbed and the percent resorbed conceptuses per litter were increased or significantly increased in the 100 mg/kg/day group. The number of early resorptions, the average number of early resorptions per litter and the percent resorbed conceptuses per litter were increased or significantly increased in the 10 and 50 mg/kg/day groups.

Embryo-fœtal development

No study on the toxicity of thalidomide on the embryo-fœtal development was conducted by the applicant. McBride and Lenz were the first to document an association between maternal thalidomide use and the increase in the incidence of limb and internal malformation of infants [22]. Thalidomide is known to cause a variety of congenital malformations, with in particular stunted development of limbs (phocomelia) or complete absence of limbs (amelia) [22, 23]. Hand deformities, finger aplasia or hypoplasia, and hip dysplasia or dislocation also occur [22, 23]. Other organs susceptible to malformation include the ears, lips, palate, eyes, heart, spine, respiratory tract, gastrointestinal tract, kidneys, and the reproductive tract [24]. In humans, the available literature does not suggest a clear developmental-no-adverse-effect-level (DNOAEL) [25]. A single 50 mg thalidomide dose or several days dosing at 25 mg taken during the sensitive period of pregnancy is sufficient to have a teratogenic effect on the developing foetus [22, 23]. This sensitive period is 21-35 days after conception, a crucial time for the development of the limbs and major organ systems [23].

Prenatal and postnatal development, including maternal function

Time-mated female rabbits (N=31) were dosed with 0, 30, 150 or 500 mg/kg from gestation day 18 through day 28 of lactation. The postnatal reproductive evaluation was conducted with the F_1 generation rabbits when they reached approximately 6 months of age.

F_0 generation rabbits: The maternal NOEL was less than 30 mg/kg as all doses resulted in abortions. Reduced absolute and relative feed consumptions were seen in the two highest dose groups. There was no effect on the length of gestation or parturition. Thalidomide milk concentrations were higher than maternal thalidomide plasma concentrations.

F1 generation rabbits: The NOEL for viability and growth in the offspring was 30 mg/kg. Doses of 150 mg/kg and 500 mg/kg caused a significant increase in pup mortality. Splayed limbs occurred in pups in all the maternal dose groups and the incidence of pups with splayed limbs exhibited a dose-related increase in the 150 and 500 maternal dose groups. The increase in the incidence of splayed limbs in the 500 mg/kg maternal dose group may have been to a treatment-related decrease in litter size resulting in superior nutritional status for rabbits in smaller litters where musculoskeletal development provided inadequate support for F1 pups with quick weight gain.

No deaths related to maternal administration of test article occurred in the F_1 generation post-weaning. Body weights were reduced in rabbits from litters where F_0 generation does were administered ≥150 mg/kg. Fertility and mating for the F_1 rabbits was affected by doses of ≥150 mg/kg to the F_0 generation.

- Local tolerance

No studies have been performed by the applicant. Thalidomide is administered via the oral route.

- Other toxicity studies

Immunotoxicity: Thalidomide has immunomodulatory and anti-inflammatory properies, which means it could have the potential to cause immunotoxicity. No findings attributable to immunotoxicity have been observed in repeat-dose toxicity studies. Immunotoxicity has not been observed in the clinical setting.

Ecotoxicity/environmental risk assessment

In the Phase I, the default values (1% market penetration) resulted in a $PEC_{SURFACEWATER}$ of 1 µg/l which would necessitate a phase II fate and effects analysis. Thalidomide is an orphan drug, and the incidence of multiple myeoloma is estimated to be 28981 patients per year. Refining the PEC based on a maximal market penetration (all multiple myeloma patients receive thalidomide) results in $PEC_{SURFACEWATER}$ = 0.0059 µg/l which is below the 0.01 µg/l threshold concentration.

The refined $PEC_{SURFACEWATER}$ for thalidomide is below the 0.01 µg/l threshold concentration, and thalidomide also has a Log Ko/w below 4.5. Taking these factors into consideration would indicate that screening for environmental fate and effects is not necessary. Thalidomide, however, has a known reproductive toxicity effect in man and some animal species. Additional consideration and studies on the environmental fate and effects analysis have therefore been undertaken:
- Thalidomide undergoes rapid degradation by hydrolysis in aqueous solution at neutral and alkaline pHs, the rate of hydrolysis increasing as the pH of the solution increases;
- The ultimate products in the hydrolytic degradation pathway of thalidomide are the amino acids glutamic acid, glutamine, isoglutamine, and phthalic acid;
- Absorbed thalidomide is eliminated from animals and humans almost exclusively by hydrolysis with subsequent elimination of the breakdown products via the urine;
- In a rat study using radioactive thalidomide, 50 to 65% of the dose (radioactivity) was excreted in the faeces at higher doses;
- In an excretion study in rhesus monkeys, 1% of radioactivity recovered from urine and faeces was unchanged thalidomide;
- Thalidomide is not biodegradable;
- Waste water used for the drug product manufacture is treated (at the site of manufacture of Pharmion 50 mg thalidomide capsules) to degrade the drug substance by increasing the pH to 14 before discharge into the sewerage system; and
- Thalidomide was found to be non-toxic to *Photobacterium phosphoreum* and fathead minnows at the highest concentration that could be tested, 45 mg/mL and 100 mg/mL, respectively.
It was concluded that thalidomide does not represent a risk to the environment.

Discussion on the non-clinical aspects

Pharmacology

The primary pharmacological actions of thalidomide described in the literature include anti-angiogenic and immunomodulatory/anti-inflammatory activity. The molecular mechanism for the pharmacology of thalidomide is unknown. The proposed mechanisms for the anti-angiogenic activity of thalidomide include (1) a down-regulation of TNF-α levels; (2) down-regulation of Vascular Endothelial Growth Factor (VEGF) expression; (3) inhibition of the response to basic Fibroblast Growth Factor (bFGF) and VEGF potentially through the modulation of integrin expression and impairment of migration; (4) inhibition of endothelial cell proliferation; and (5) blocking of cyclooxigenase-2 (COX-2) induction. Thalidomide has been shown to be efficacious in several animal models of immune-mediated and pain induced inflammatory disorders and TNF-α-induced conditions. Thalidomide has been show to induce apoptosis in human peripheral blood monocytes and to inhibit NF-κB. Thalidomide has been shown to induce apoptosis or growth arrest in several Multiple Myeloma (MM) cell lines. In animal models of MM, thalidomide demonstrated some evidence of anti-angiogenic activity as well as directly inhibiting myeloma growth. It is considered that the non-clinical data give some support for the use of thalidomide in multiple myeloma.

The main secondary pharmacodynamic activity of thalidomide concerns it's central nervous system (CNS) activity, as exemplified by the initial use of thalidomide as a sedative in Europe. Safety pharmacology studies with thalidomide are limited. Thalidomide shows no relevant activity on the

hERG channel. The lack of a full safety pharmacology program is acceptable, given the clinical experience.

Pharmacokinetics

The choice of the racemate instead of a single enantiomer is justified by the interconvertion, especially since it leads to racemisation. The equilibrium of epimerisation and the rate to reach this equilibrium depend respectively on the pH and on the temperature. Thalidomide interconverts between the R(+) and S(-) enantiomers in plasma and is about 55-65% plasma protein bound. The interconversion of enantiomers poses a specific question. The classic rules which are based on the hypothesis of the irreversible elimination of the product by excretion or metabolism are not applicable. Estimation and interpretation of the individual parameters of each enantiomer can only be achieved by independent administration of each enantiomers and measurement of concentrations of both. In the animal studies only thalidomide racemate was administered, and the assay methods were not enantiospecific. Therefore, results can only be descriptive. The calculation of pharmacokinetic parameters, clearance and volume of distribution, bioavailability of each enantiomer are not possible.

The pharmacokinetics of thalidomide following oral doses are nonlinear with a plateau effect seen in C_{max} and $AUC_{(0\text{-}24hr)}$, across all species. The data suggest a saturation of absorption due to the low solubility of thalidomide in the gastrointestinal tract. No clear differences were seen between males and females across all species.

Thalidomide is distributed into animals' milk and semen. The latter finding has been taken into consideration when establishing contraception requirements for adult male patients (see SPC sections 4.4, 4.6, and clinical pharmacokinetics). Breast-feeding should be discontinued during therapy with thalidomide.

Metabolism of thalidomide is negligible and the large number of hydrolysis products found in urine are those formed by the spontaneous hydrolysis of thalidomide. Interactions between thalidomide and other drugs are unlikely. More than 90% of the absorbed drug is excreted in urine and faeces, almost entirely in the form of hydrolysis products and/or metabolites.

Toxicology

There is no available single dose toxicity studies, however, the clinical data provided or from the literature indicate that acute toxicity of thalidomide is quite low.

Repeat-dose toxicity studies showed:

- discoloured urine in mice and dogs (likely due to the excretion of degradation products of thalidomide such as α-aminoglutarimide); in the male dog, after one year of dosing, reversible bile plugs in canaliculi were observed at exposures greater than 1.9 fold the human exposure;

- decreased platelet count in mice and rats (safety margin: 2.4 in the rat based on AUC at the NOAEL), likely to be species specific as no decrease in platelet counts were reported in humans;

- increased liver weight associated to a centrilobular hepatocellular hypertrophy. As claimed by the applicant, a link with hepatocellular metabolizing enzyme induction might explain this effect. However, pharmacokinetic data did not provide any demonstration of such induction (thalidomide very slightly interacts with CYP and the major degradation pathway of thalidomide is spontaneous hydrolysis in aqueous medium). The safety margin is less than 0.3 based on the results in the mouse and 12 in the rat;

- - no effects of thalidomide on thyroid function in dogs. I n rats, there was an apparent dose-dependent decrease in total and free T4 that was more consistent in the female;

- enlarged and/or blue discoloration of mammary glands and prolonged oestrus in female dogs at exposures equal to 1.8 or greater than 3.6-fold the human exposure, respectively. The relevance to humans is unknown;

- no changes consistent with peripheral neuropathy in rats or dogs;

- no signs of immunotoxicity.

Thalidomide is considered not genotoxic as it was negative in the Ames/Salmonella-E. coli reverse mutation assay, in the AS52/XPRT mammalian cell forward gene mutation assay and in the *in vivo* micronucleus test in mouse bone marrow erythropoietic cells.

No evidence of carcinogenicity was observed at exposures approximately 15, 13 and 39 times the estimated clinical AUC at the recommended starting dose in mice, male rats and female rats respectively.

Animal studies have demonstrated differences in species susceptibility to the teratogenic effects of thalidomide. In humans, thalidomide is a proven teratogen (see SPC section 4.3, 4.4 and 5.3). It was considered acceptable that no additional non-clinical study was performed. A study in rabbits demonstrated no effect on fertility indices in males or females although testicular degeneration was observed in males. A peri and postnatal toxicity study performed in rabbits with thalidomide administered at doses up to 500 mg/kg/day resulted in abortions, increased stillbirths and decreased pup viability during lactation. Pups from mothers treated with thalidomide had increased abortions, reduced body weight gain, alterations in learning and memory, decreased fertility, and reduced pregnancy index.

Thalidomide Pharmion 50 mg capsules do not represent a risk to the environment primarily due to the propensity of the drug substance to hydrolyse at pH values greater than 6.0 and the calculated $PEC_{SURFACEWATER}$ for thalidomide is below the 0.01 µg/l guideline [26] threshold concentration.

1.4. Clinical aspects

Introduction

The clinical programme of thalidomide comprised single-dose pharmacokinetic studies generated from healthy volunteers (THA I EU 2004 BA 001, Thal-BA-001, PK-001, PK-003, PK-004, PK-006, and PK-007) and from patients with Hansen's disease (PK-005) and HIV-seropositive patients (PK-UK001). Multiple-dose pharmacokinetic data were evaluated in 3 drug-drug interaction studies (PK-003, Thal-PK-011, and Thal-PK-012).
In the initial submitted application, the applicant claimed the following two therapeutic indications:
"*Thalidomide Pharmion in combination with melphalan and prednisone for the treatment of patients with untreated multiple myeloma ≥ 65 years or ineligible for high dose chemotherapy", and "Thalidomide Pharmion in combination with dexamethasone for induction therapy prior to high dose chemotherapy and bone marrow transplant, for the treatment of patients with untreated multiple myeloma*". The clinical efficacy data supporting the therapy of patients with previously untreated multiple myeloma ≥ 65 years or ineligible for high-dose chemotherapy was based on a phase III randomised, open label pivotal study conducted by the Intergroupe Francophone du Myélome (IFM) The IFM 99-06 study enrolled previously untreated multiple myeloma (MM) patients aged 65 to 75 years. Patients were randomized to the MP, MPT, and MEL100 treatment groups in a 3:2:2 ratio. Supportive efficacy data was provided by the publication of the GISMM2001 study conducted by the Gruppo Italiano Malattie Ematologiche dell' Adulto (GIMEMA) cooperative group. The GISMM2001 study was a randomized, open-label, controlled, multicenter study comparing Thalidomide Pharmion in combination with MP versus MP alone in patients who were older than 65 years of age (or younger patients unable to undergo transplantation) with newly diagnosed multiple myeloma.
For the use of thalidomide with dexamethasone for induction therapy of untreated multiple myeloma, two multicenter, open label, controlled, parallel group Phase III studies were submitted, including a company sponsored THAL-MM-003 study and the E1A001 study conducted by the Eastern Cooperative Oncology Group (ECOG). **This indication was withdrawn during the procedure of assessment of the application.**

The company-sponsored clinical trials were performed in accordance with GCP as claimed by the applicant. The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.
Thalidomide treatment must be initiated and monitored under the supervision of physicians with expertise in managing immunomodulatory or chemotherapeutic agents and a full understanding of the risks of thalidomide therapy and monitoring requirements. The recommended oral dose is 200 mg per day. Thalidomide should be taken as a single dose at bedtime, to reduce the impact of somnolence and

can be taken with and without food. When thalidomide is used in combination with melphalan and prednisone, a maximum number of 12 cycles of 6 weeks should be used. Patients should be monitored for thromboembolic events, peripheral neuropathy, rash/skin reactions, bradycardia, syncope and somnolence (see SPC sections 4.2, 4.4 and 4.8). Dose delay, reduction or discontinuation, dependent upon the NCI CTC grade, may be necessary.

Pharmacokinetics

Pharmacokinetic (PK) plasma samples from clinical studies were analysed for thalidomide parent compound using validated high performance liquid chromatography (HPLC) methods. In Study PK-005, a liquid chromatography/mass spectrometry (LC/MS) method was used to analyse thalidomide and its potential metabolites, 3-OH-thalidomide, 4-OH thalidomide, and N-OH-thalidomide, in plasma and urine, at concentrations of 50 to 5000 ng/ml. HPLC/LC-MS/MS methods were used to determine thalidomide levels in human heparinised plasma in studies PK-007, PK-UK008, Thal-BA-001, THA I EU 2004 BA 001 and LA TH 03-01 and human semen in study PK-UK008.

- Absorption

Bioavailability
The relative bioavailability of two different thalidomide capsules (the commercial capsule *versus* IFM 99-06 clinical trial capsule) was assessed after single oral administration in 18 healthy volunteers in a randomized, open-label, two-way crossover pivotal bioavailability study (THA I EU 2004 BA 001). The mean Cmax and AUC values were comparable between the two formulations, as confirmed by the points estimate (1.05 for Cmax and 1.01 for AUC values) and the 90% confidence intervals (CIs) which were inside the bioequivalence range (0.80 to 1.25) for both Cmax and AUC. Tmax occurred earlier after dosing with the commercial capsule compared to the IFM 99-06 clinical trial capsule (2.5 *versus* 3.5 hours, respectively). The mean terminal half-life was comparable between formulations (7.05 and 6.99 hours for the IFM 99-06 clinical trial and commercial capsule, respectively). Overall, the mean relative bioavailability of thalidomide capsules was 1.01 ± 0.07 based on AUC(0-∞). Thus, the commercial thalidomide 50 mg capsule formulation was bioequivalent to the IFM 99-06 clinical trial thalidomide 50 mg capsule formulation in regard to extent of absorption and overall exposure of thalidomide.

The absolute bioavailability of thalidomide has not been determined in humans. However, thalidomide has been shown to be slowly absorbed from the gastro-intestinal tract following oral administration with peak plasma concentrations occurring 1 to 5 hours after dosing. The drug disappears from plasma monophasically with a terminal half-life of approximately 7 hours.

Bioequivalence
Study PK-001 was a single center, randomized, open-label, 3-way crossover study which evaluated the bioequivalence of 3 formulations of thalidomide capsules; commercial formulation, clinical trial formulation, and a widely used capsule formulation manufactured by the Brazilian manufacturer, Tortuga. A total of 17 healthy male subjects, aged 20 to 43 years, were enrolled and completed the study. On Day 1 of each period, each subject received one of the following treatments: a single oral 200 mg (4 x 50 mg) dose of thalidomide, administered as commercial formulation capsule; a single oral 200 mg (4 x 50 mg) dose of thalidomide, administered as clinical trial formulation capsule; a single oral 200 mg (2 x 100 mg) dose of thalidomide, administered as alpha-phthalimidoglutarimide Tortuga capsule. Pharmacokinetic results showed the commercial formulation and the clinical trial formulation to be bioequivalent. The Tortuga formulation was not bioequivalent with either formulation.

Study PK-007 was a single center, randomized, open-label, 3-way crossover study which assessed the bioavailability of two formulations of thalidomide (tablet and capsule) relative to an oral liquid solution formulation. The thalidomide tablet and capsule were bioequivalent to each other with respect to Cmax, AUC(0-t), and AUC(0-∞).

Study Thal-BA-001 was a single center, randomized, open-label, 2-way crossover study which investigated the relative bioavailability of 2 different oral formulations of thalidomide: commercial formulation and Grünenthal tablet. Overall systemic exposure to thalidomide [AUC(0-∞)] was similar for capsules and tablets, with the 2 formulations being shown to be bioequivalent, mean Cmax was

approximately 27% higher for the capsule compared to the tablet and the mean terminal elimination half-life of thalidomide was similar for the capsule and the tablet (6.9 and 7.6 hours, respectively).

Influence of food
Study PK-006 was a single center, randomized, open-label, 3-way crossover study conducted to determine the effect of food on the Celgene (Synovir) 50 mg capsule (commercial formulation), and to assess the relative bioavailability of the Celgene 50 mg capsule (commercial formulation) with the Serral, S.A. de C.V. 100 mg tablet when both were administered in a fasting state.

The effect of food on Cmax, AUC(0-t), and AUC(0-∞) was minor (decreasing or increasing by less than 9%), while the effect of food on mean Tmax was significant (increasing by 61.8%).The Synovir™ thalidomide capsule formulation showed a comparable but greater relative bioavailability with respect to AUC(0-t) and AUC(0-∞) (mean ratios of 122% and 110%, respectively), and showed a 2-fold larger Cmax (mean ratio of 194%) when compared with the Serral, S.A. de C.V. thalidomide tablet formulation. Co-administration of food delayed absorption but did not alter the overall extent of absorption. Thus, no restrictions on food intake relative to thalidomide dosing are recommended.

Single dose PK
Study PK-004 was a single center, randomized, open-label, 3-way crossover study to characterize the single dose PK of thalidomide and to assess dose proportionality over the clinical dose range of 50 to 400 mg. On Day 1 of each period, each subject received 1 of the following treatments: a single oral 50 mg dose of thalidomide administered as Celgene Synovir capsule; a single oral 200 mg (4 x 50 mg) dose of thalidomide administered as Celgene Synovir capsule; and a single oral 400 mg (8 x 50 mg) dose of thalidomide administered as Celgene Synovir capsule. A total of 15 healthy subjects (14 male, 1 female), aged 20 to 54 years, were enrolled. A total of 14 subjects received 50 mg thalidomide; 15 subjects received 200 mg thalidomide; and 14 subjects received 400 mg thalidomide. Thalidomide was dose proportional in terms of AUC(0-∞) over the dose range from 50 to 400 mg. Cmax did not increase proportionally over the same range.

Study PK-UK001 was a single center, open-label, randomized, 2-way crossover study to assess PK and dose proportionality of thalidomide administered as a single dose of 100 and 200 mg to male volunteers who were HIV-seropositive. The overall PK of thalidomide follow a 1-compartment model with first-order absorption and elimination. The PK parameters were similar when thalidomide 50 mg capsules were administered as either two capsules (100 mg) or four capsules (200 mg). Values of Tmax and absorption kinetic parameters were variable and showed a trend towards slower oral absorption after the 200 mg dose of thalidomide.

Multiple dose PK
Study PK-003 was a single center, randomized, open-label, 2-way crossover study to evaluate the effect of steady-state concentrations of thalidomide on the PK of ethinyl estradiol and norethindrone, and to evaluate the effect of multiple dose thalidomide PK. Pharmacokinetic results showed similar thalidomide PK profiles after the first dose and after 18 days of dosing. Clearance and AUC for both ethinyl estradiol and norethindrone were not significantly altered following 20 days of 200 mg/day thalidomide to premenopausal healthy females.

- Distribution

The thalidomide R(+) and S(-) enantiomers were respectively 55% and 65% bound to plasma proteins. Plasma protein binding of racemic thalidomide has not been determined. In study PK-UK008, two HIV-seropositive male patients receiving thalidomide 100 mg/day for 8 weeks, had detectable levels of thalidomide found in semen (10 to 250 ng/g). Similar levels of drug (10 to 350 ng/ml) were found in plasma samples taken at approximately the same time. These findings suggest that contraceptive precautions are necessary in partners of males taking thalidomide.

- Elimination

Metabolism
Thalidomide is eliminated almost exclusively by spontaneous (non-enzymatic) hydrolysis. There is minimal hepatic metabolism of thalidomide. *In vitro* studies demonstrated that thalidomide does not appear to undergo significant metabolism by human cytochrome P450 (CYP). In study PK-005, pharmacokinetics were assessed by measuring serial plasma concentrations of thalidomide and the metabolites 3-OH-thalidomide, 4-OH-thalidomide, and N-OH-thalidomide. Although parent

thalidomide was quantifiable at maximum concentrations of 3400 ng/ml, none of the expected metabolites were observed in the plasma (lower limit of quantitation of all compounds was 50 ng/ml).

Excretion
The mean elimination half-life of thalidomide at single doses of 50 to 400 mg was between 5 and 7 hours. In Study PK-005, thalidomide and 4-OH-thalidomide were excreted in the urine (< 1% and < 0.01% of the dose, respectively).

Inter-conversion
Thalidomide proposed for this application is a racemic mixture that contains equal amounts of the S(-) and R (+) enantiomers. The mean half-lives of *in vitro* degradation are 4.3 and 3.8 hours for the R(+)- and S(-) enantiomers, respectively. The *in vivo* rate of inter-conversion half-life is 2.3 hours.

- Dose proportionality and time dependencies

Over a dose range of 50 to 400 mg, AUC values increased proportionately with dose but Cmax did not, suggesting that at higher doses, the drug may be absorbed at a slower rate (studies PK-004 and LA/TH 98006 conducted in post-menopausal women receiving single doses of 50, 100 and 200 mg as 50 mg capsules under fasting conditions)

Intra- and inter-individual variability
In study THA I EU 2004 BA 001, coefficients of variation (CV%) for AUC(0-∞) and Cmax were low suggesting a low inter-individual variability. Intra-individual variability has not been investigated.

- Special populations

No specific PK study has been conducted in target population i.e. patients with multiple myeloma.

Impaired renal function: The pharmacokinetics of thalidomide has not been specifically studied in patients with varying degrees of renal impairment. Study GKTH-01 was a single center, open-label, 2 phase, multiple-dose study to compare thalidomide clearance in hemodialysis patients; during hemodialysis and on days when patients were not undergoing hemodialysis. In these patients while off-dialysis, clearance of thalidomide was estimated to be 7.7 l/h. On-dialysis, the clearance was 19.6 l/h. Analyses showed that as thalidomide is taken at bedtime, most of the drug would be eliminated prior to a dialysis session.

Impaired hepatic function: The effects of hepatic impairment on the pharmacokinetics of thalidomide have not been studied in humans. Thalidomide undergoes spontaneous non-enzymatic hydrolysis, and its metabolism is not expected to be affected by an alteration in hepatic enzymes or hepatic dysfunction. *In vitro* and *in vivo* studies showed that hepatic cytochrome P-450 enzymes do not play a significant role in the metabolism of thalidomide (see non-clinical section).

Pharmacokinetic differences due to gender, weight, ethnic group, have not been studied. No specific PK data are available in paediatric or elderly patients. However, clinical experience in elderly patients with MM participating in clinical studies IFM 99-06, THAL-MM-003, and E1A001 has adequately characterized the safety profile of thalidomide ion this population [71.4% (798/1117) of patients were aged > 65 years].

- Pharmacokinetic interaction studies

Oral Contraceptives
In study PK-003, the effect of single and multiple dose thalidomide 200 mg/day on oral contraceptives (0.035 mg ethinyl estradiol and 1 mg norethindrone) was examined. Clearance and AUC for both ethinyl estradiol and norethindrone were not significantly altered following 20 days of continuous dosing with thalidomide 200 mg/day.

Digoxin
In study Thal-PK-011, the effect of thalidomide 200 mg/day for 7 days on the pharmacokinetics of a single, oral 0.5 mg dose of digoxin was examined. Thalidomide had no effect on the pharmacokinetics of digoxin. In addition, single-dose administration of 0.5 mg digoxin had no effect on thalidomide pharmacokinetics.

Warfarin
In study Thal-PK-012, the effect of thalidomide 200 mg/day for 9 days on the pharmacokinetics of a single, oral 25 mg dose of warfarin was examined. Thalidomide had no effect on the pharmacokinetics

of warfarin (both S-warfarin and R-warfarin), and had no effect on the international normalized ratio (INR). In addition, single-dose administration of 25 mg warfarin had no effect on thalidomide pharmacokinetics.

Medicinal products known to cause deep vein thrombosis
There is an increased risk for thrombo-embolic events when thalidomide is taken with other anti-myeloma medications such as melphalan, doxorubicin, and dexamethasone [27-31]. The incidence of DVT in patients treated with thalidomide alone is < 5% compared with an incidence of 10% to 12% when thalidomide is given concomitantly with either dexamethasone or melphalan and an incidence of approximately 25% when given with other cytotoxic chemotherapeutic agents, particularly doxorubicin. Based on these findings, consideration should be given to the use of prophylactic anticoagulation in patients treated for conditions known to be associated with a significant risk for thrombosis.

A correlation has been reported between the occurrence of thrombosis and treatment with lenalidomide (an analogue of thalidomide) and high-dose dexamethasone when given concomitantly with erythropoietin. Preliminary findings from a multivariate analysis of data showed that of the patients treated with the lenalidomide/dexamethasone combination who also received erythropoietin therapy, 23% experienced thrombosis compared with 5% who did not receive erythropoietin. Because of similarities between lenalidomide and thalidomide, to further explore this theory, the relationship between events of DVT and the use of erythropoietin concomitantly with the combination of thalidomide/dexamethasone was evaluated in Study THAL-MM-003. The number and percent of patients with 1 or more DVT/PE events was found to be higher in users vs. non-users for the thalidomide/dexamethasone group (24.4% vs. 17.6%, respectively); in the placebo/dexamethasone group, the incidence was comparable for the users and non-users (5.3% and 5.7%, respectively). The number of patients who used erythropoietin concomitantly in this study, however, was low in both treatment groups (41/234 users in the thalidomide/dexamethasone and 38/232 in the placebo/dexamethasone).

Medicinal products known to cause peripheral neuropathy
Medicinal products known to be associated with peripheral neuropathy (e.g. vincristine and bortezomib) should be used with caution in patients receiving thalidomide. The use of thalidomide for the management of mucocutaneous disorders in HIV-infected patients should be limited as it can increase the neuropathic effects of zalcitabine, didanosine, and stavudine.

Sedatives
Thalidomide is known to enhance the sedative effects of barbiturates, alcohol, chlorpromazine, and reserpine.

Pharmacodynamics

- Mechanism of action

No human pharmacodynamic studies have been conducted by the applicant. However, the pharmacodynamic effects of thalidomide are largely documented in published literature. The main pharmacological actions of thalidomide include anti-angiogenic and immunomodulatory/anti-inflammatory activity (see also non-clinical pharmacology).

Immunomodulation: Several mechanisms may be involved including suppression of monocyte inflammatory cytokine production, enhancement of T cell and natural killer (NK) cell responses, down-regulation of selected cell-surface adhesion molecules involved in leucocyte migration and shifts in the ratio of CD4+ lymphocytes (helper T-cells) to CD8+ lymphocytes (cytotoxic T-cells).
In monocytes, thalidomide inhibits pro-inflammatory cytokine tumour necrosis factor (TNF)-α and interleukin (IL)-12 white cells elevating production of the anti-inflammatory cytokine IL-10. Thalidomide is generally co-stimulatory to T cells, enhancing cell proliferation and production of IL-2 and interferon IFN-γ in both CD4+ lymphocytes (helper T cells) and CD8+ lymphocytes (cytotoxic T cells), with a greater effect on the CD8+ subset. The cytolytic activity of natural killer (NK) cells was augmented by thalidomide in vitro, as were the numbers of circulating NK cells and plasma IL-2 and IFN-γ levels in multiple myeloma patients on thalidomide therapy. Peripheral blood mononuclear cells (PBMC) from subjects dosed with thalidomide showed an increase in IFN-γ production and a decrease in IL-5 production ex vivo, suggesting a tendency of the drug to shift the cytokine balance

toward a Th1-type response. However thalidomide treatment of normal PBMC in vitro caused inhibition of IFN-γ production and enhancement of IL4 and IL5 production suggesting a shift towards a Th2-type immune response. Therefore, the Th1/Th2 balance of a system may shift in response to thalidomide according to the cellular environment and specific stimuli. Similarly, thalidomide has been shown to increase plasma TNF-α in HIV-seropositive patients.

Cellular immunity: Mast cells, neutrophils and TNF-α are closely related in the pathogenesis of the inflammatory reactions. In vitro studies have shown thalidomide to inhibit neutrophil chemotaxis to the site of inflammation. This effect could be explained by the blunted expression of the cell-surface adhesion molecules, E-selectin, ICAM-1 and VCAM, on endothelial cells in the presence of thalidomide. Although contradictory data have been published, thalidomide treatment has been reported to reduce the number of neutrophils in skin lesions of ENL patients.

Anti-angiogenesis: Proposed mechanisms for the anti-angiogenic activity of thalidomide include: a down-regulation of tumour necrosis factor-alpha (TNF-α) levels; down-regulation of vascular endothelial growth factor (VEGF) expression; inhibition of the response to basic fibroblast growth factor (bFGF) and VEGF potentially through the modulation of integrin expression and impairment of migration; inhibition of endothelial cell proliferation; blocking of cyclooxigenase-2 (COX-2) induction.

- Primary and Secondary pharmacology

The precise mechanism of action of thalidomide in the treatment of multiple myloma has not been defined. In one clinical study in patients with multiple myloma, thalidomide decreased the micro-vessel density and hence, had some anti-angiogenic effects. However, it has also been reported that three quarters of patients who respond to a thalidomide regimen do not show alterations in their microvessel density.

The main secondary pharmacodynamic activity of thalidomide concerns its central nervous system (CNS) activity. As thalidomide was initially approved in Europe as a sedative, the CNS properties of this product are well known.

The potential of thalidomide to prolong the QT interval has been investigated in company-sponsored studies on hERG channels and in dog isolated Purkinje fibre preparations. Thalidomide has been shown to cause bradycardia (see also clinical safety).

Discussion on clinical pharmacology

The pharmacokinetics of thalidomide is characterised by a slow absorption after oral administration from the gastro-intestinal tract. The maximum plasma concentrations are reached 2-5 hours after administration. Co-administration of food delays absorption but does not alter the overall extent of absorption. There is a rapid *in vivo* rate of inter-conversion with a half-life of 2.3 hours. The plasma protein binding of the (+)-(R) and (-)-(S) enantiomers was found to be 55% and 65% respectively. Thalidomide is present in the semen of male patients at levels similar to plasma concentrations. Therefore, because of the known severe teratogenic effects of the product, during treatment with thalidomide and for 1 week after stopping the treatment, male patients must use condoms if their partner is pregnant or is of childbearing potential not using effective contraception (see SPC sections 4.4, 5.2). The exact metabolic route and fate of thalidomide is not completely known in humans. Available data indicate that the medicinal product is eliminated mainly by non-enzymatic hydrolysis. There is minimal cytochrome P450 catalysed hepatic metabolism of thalidomide. There are *in vitro* data indicating that prednisone may give rise to enzyme induction which could reduce the systemic exposure of concomitantly used medicinal products. The *in vivo* relevance of these findings is unknown. Thalidomide does not interact with digoxin. It is not known whether the effect will be different in multiple myeloma patients. The urinary excretion of thalidomide, as unchanged drug, is negligible, the major route of excretion of thalidomide is non-renal. The mean elimination half-life of thalidomide in plasma following single oral doses between 50 mg and 400 mg was 5.5 to 7.3 hours. Total systemic exposure (AUC) is proportional to dose at single-dose conditions. No time dependency of the pharmacokinetics has been observed. The applicant has agreed to conduct a study to clarify the route and fate of elimination of thalidomide. Upon review of the data generated during this study, appropriate sections of the SPC (i.e. 4.2, 4.4, and 5.2) will be updated. In addition, the applicant has

committed to provide population pharmacokinetic and pharmacodynamic information in the target population (MM patients).

Thalidomide Pharmion has not formally been studied in patients with impaired renal or hepatic function. The pharmacokinetics of thalidomide in patients with impaired renal or hepatic function is unknown. No specific dose recommendations for these patient populations are available. Patients with severe organ impairment should be carefully monitored for adverse reactions. No specific dose adjustments are recommended for the elderly.

No human pharmacodynamic studies have been submitted. However, the pharmacodynamic effects of thalidomide have been extensively documented in the published literature. The main pharmacological actions of thalidomide include anti-angiogenic and immunomodulatory/anti-inflammatory activity.

Thalidomide has sedative properties thus may enhance the sedation induced by anxiolytics, hypnotics, antipsychotics, H1 anti-histamines, opiate derivatives, barbiturates and alcohol. Caution should be used when thalidomide is given in combination with medicinal products that cause drowsiness.

Thalidomide does not interact with hormonal contraceptives. However, combined hormonal contraceptives are not recommended due to the increased risk of venous thrombo-embolic disease (see SPC section 4.4). Due to the potential of thalidomide to induce bradycardia, caution should be exercised with medicinal products having the same pharmacodynamic effect such as active substances known to induce torsade de pointes, beta blockers or anticholinesterase agents.

Clinical efficacy

A summary of the main studies supporting this application (provided as study reports or publication) is provided in the table below.

Table 11: Summary of design and population characteristics of the studies included in the submission

Characteristic	MP + Thalidomide		Dex + Thalidomide	
	IFM 99-06	GISMM2001 (publication)	THAL-MM-003	E1A00
Design	International, multicenter, randomized, open-label, controlled, Phase III (pivotal)	Multicenter, randomized, open-label, controlled, Phase III	International, multicenter, randomized, double-blind, placebo-controlled, Phase III (pivotal)	Multicenter, randomized, open-label, controlled Phase III
Population	≥ 65 to ≤ 75 years (or < 65 but not eligible for treatment intensification protocol with bone marrow suppression conditioning), stage II or III per DS (stage I if high progressive potential), and no prior treatment for MM 447 pts randomized	> 65 years with DS stage II or III MM (younger if unable to undergo transplantation) 255 pts randomized	≥ 18 years with diagnosis of MM, DS stage II or III, and no prior treatment with systemic antimyeloma therapy (prior radiotherapy okay) 470 pts randomized	≥ 18 years with recent diagnosis of MM, no prior treatment 207 pts randomized

Abbreviations: Dex: dexamethasone; DS: Durie and Salmon classification [32]; MM: multiple myeloma ; MP: melphalan/prednisone.

- Dose response studies

Based on the data from the literature [33] and from experience with thalidomide, a strategy of starting at 200 mg/day and increasing to a maximum of 400 mg/day, depending upon tolerability, was used in study IFM99-06. In study GISMM2001, thalidomide was administered at a fixed dose of 100 mg/day, with a dose reduction to 50 mg/day based on tolerability. In addition to using a lower dose, thalidomide was also administered over fewer cycles of shorter duration (6 cycles of 4 weeks) compared with study IFM99-06. In study THAL-MM-003, the thalidomide dose was to be escalated from 50 mg/day from days 1 to 14 of cycle 1, to 100 mg/day from days 15 to 28, and administered at 200 mg/day from cycle 2 onwards. The overall median daily dose was 200 mg (mean 149.6 mg) and

the median final daily dose was 200 mg (mean 165.0 mg). In the E1A00 study, thalidomide/dexamethasone was started at 200 mg for four 28-day cycles. The median daily dose of thalidomide was 196.4 mg (mean 169.7 mg) over all treatment cycles.

- Main study

IFM 99-06

METHODS

Study Participants
This was a randomised, open-label, controlled, phase III trial. The main inclusion criteria were patients with MM [defined as per the Southwest Oncology Group (SWOG) criteria] [34] never previously treated for MM; aged between 65 and 75 years, or age less than 65 years, but not eligible for a treatment intensification protocol with bone marrow suppression conditioning; MM of stage II or III as per the Durie and Salmon (DS) classification [32] or presenting with DS Grade I myeloma with high progressive potential defined as follows: DS Grade I myeloma with the presence of a painful or non-painful bone lesion imaged by standard X-ray; DS Grade I myeloma with painful bone site lesion documented by radiology irrespective of the method of radiological investigation [in particular, magnetic resonance imaging (MRI) documented bone lesion if the lesion is painful]; DS Grade I myeloma presenting with 2 or 3 of the following characteristics in addition to the first: hemoglobin (Hb) < 12 g/dl in males or < 11 g/dl in females, bone marrow plasmacytosis > 25%, serum monoclonal component >30 g/l for immunoglobulin G (IgG), >25 g/l for IgA (defined by serum protein electrophoresis) or > 1 g/24h for Bence Jones' (BJ) proteinuria; DS Grade I myeloma with bone marrow plasmacytosis > 25% and/or serum monoclonal component > 30 g/L (IgG), > 25 g/l (IgA) or > 1 g/24 h (BJ) combined with weight loss of >5% of the body weight over the year and/or > 1 documented infection due to Gram+ cocci or Gram – bacilli in the year. Patients with kidney failure with serum creatinine ≥ 50 mg/l (450 µmol/l), impaired cardiac condition, or significant impairment of hepatic function were not to be included in the study.

Treatments
Patients were randomized to either arm A: conventional treatment melphalan/prednisone (MP), arm B: conventional treatment plus thalidomide (MPT), or arm C: intensive treatment.

In arm A: MP (melphalan: 0.25 mg/kg/day; prednisone: 2 mg/kg/day) were administered orally every 6 weeks from day 1 to day 4. In the absence of disease progression, 12 courses were given. The prednisone was administered in accordance with the standard practices at each center. Patients who developed a complication necessitating permanent withdrawal of treatment were to be withdrawn from the study, but follow-up was continued. Further treatment was left to the investigator's discretion.

In arm B: The MP treatment was identical to that for arm. In addition, patients were to receive continuous oral treatment of thalidomide at the maximum tolerable dosage, without exceeding 400 mg/day. The starting dose was 200 mg/day (single dose at night). After 2 to 4 weeks the dose could be increased to 400 mg/day (as a single dose or divided into 2 doses). However, the initial dose and subsequent thalidomide dosage adjustments were left to the investigator’s discretion. In the absence of toxicity, thalidomide was administered throughout the duration of MP chemotherapy, until day 4 of the twelfth course. The emergence of symptomatic peripheral neuropathy, confirmed by electromyogram, gave rise to permanent withdrawal of thalidomide.

In arm C: patients were to receive 2 courses of VAD (each from day 1 to day 4), separated by an interval of 4 weeks. Dosage was adjusted according to age. Four weeks after the second course of VAD, if patients did not meet any of the non-intensification criteria, peripheral blood stem cells (PBSC) were mobilized by administration of 3 g/m2 cyclophosphamide with subsequent mesna (sodium 2-mercaptoethane sulphonate), day 0. G-CSF was administered subcutaneously at a dose of 10 µg/kg/day from day +1 until the last day of cytapheresis, which was initiated when the neutrophil count was ≥ 4 x 109/l. In the absence of any non-intensification criteria, the subjects were then to receive 2 intravenous courses of melphalan 100mg/m2 (MEL100). VAD consisted of vincristine: 0.4 mg and adriblastine (doxorubicin): 9 mg/m2 as a continuous infusion over 24 hours for 4 consecutive days (days 1 to 4), dexamethasone: 40 mg/day for 4 consecutive days (days 1 to 4), administered by the oral or IV route.

Prednisone therapy was administered in accordance with the standard practices at each center. If adverse effects (minor neuropsychological disorders, glucoregulation disorders or moderate hypertension) occurred, the investigator could reduce the dexamethasone dosage by 50% (i.e., 20 mg/day on 4 consecutive days). The second course of VAD was postponed for 1 week if the neutrophil count was < 1500/mm3 and/or the platelet count was < 100,000/mm3. IV cyclophosphamide was administered on Day 0 at a dosage of 3 g/m2 with fluid supplementation in combination with mesna, as per the procedures used in each center. No dosage adjustment for the course of cyclophosphamide was scheduled. G-CSF was administered SC at a dosage of 10 µg /kg/day. G-CSF was to be initiated on the day after cyclophosphamide administration (Day +1) and continued until the end of the cytaphereses. Cytaphereses were initiated when the neutrophil count was ≥ 4 x 109/l. The cytaphereses were implemented daily until at least ≥ 4 x 10^6 CD34+ cells/kg had been harvested or a maximum of 4 cytaphereses had been conducted. The harvested cells were cold-stored as per the procedure in each center. The first course of MEL100 was administered 4 to 6 weeks after cyclophosphamide, providing that no non-intensification criteria had been met. Melphalan was administered at a dosage of 100 mg/m2 by infusion over 30 minutes with fluid supplementation. No dosage adjustment for the MEL100 courses was scheduled. A minimum of 2 x 10^6 CD34+ cells/kg was re-infused 36 hours after melphalan administration. G-CSF was initiated on Day +5 at a dosage of 150 µg/m2 and continued until the neutrophil count was ≥ 1,000/mm3 on 3 consecutive days.

The second course of MEL100 was administered 2 months after the first course, providing that no non-intensification criteria had been met. Patients were required to have achieved satisfactory hematological recovery following the first course of MEL100, indicated by a leukocyte count ≥ 3,000/mm3 and a platelet count ≥ 100,000/mm3. The second course of MEL100 was identical to the first. A minimum of 2 x 10^6 CD34+ cells/kg was re-infused. G-CSF was initiated on Day +5 at a dosage of 150 µg/m2 and continued until the neutrophil count was ≥ 1,000/mm3 on 3 consecutive days. Hematological intensive care (transfusions, antibiotic and antifungal treatment) was administered as per the procedures of each center.

Objectives

The primary objective was to evaluate the efficacy (survival) of thalidomide in combination with the standard MP regimen, as compared with the use of VAD+high dose melphalan with ABMT, in patients with previously untreated MM, aged 65 to ≤ 75 years (or < 65 but not eligible for treatment intensification protocol with bone marrow suppression conditioning). The secondary objectives were to compare the best response rate, the progression-free survival (PFS) and the survival after progression, and safety in patients treated with MPT or with MEL100 or with MP as first-line therapy for patients with previously untreated MM aged 65 to 75 years.

Outcomes/endpoints

The primary endpoint was overall survival (OS) and was defined as the time (months) from randomisation to death from any cause. Patients were censored at the last date that they were known to be alive whether they were still alive at the time of analysis or were lost to follow-up before death.

The secondary outcome measures included Progression free survival (PFS) defined as the time from randomization to first progression or death from any cause, whichever occurred first. Patients were censored at the last date that the patient was known to be alive without disease progression, or at the data cut-off date (08 October 2005), whichever occurred first.

Estimate of the objective tumor response rates (CR, VGPR, PR, MR). The achievement of any response required an improvement in serum and urine monoclonal (M) protein, supported by an improvement or no worsening of bone pain and performance status, correction of hypercalcaemia, and no increase in size or number of lytic bone lesions. Definitions for the different levels of response are described below. These definitions were the standard criteria used by IFM at the time of study initiation and had been developed by IFM based on the data available at that time. During the study, the level of response at each evaluation (i.e. 3, 6, 12, and 18 months) was to be reported on the CRF. These assessments of response were reviewed centrally by the coordinating PI to ensure consistency across the study. Confirmation of response was not required as part of the response definition. Laboratory measurements were performed locally at each evaluation. Skeletal radiography was to be performed locally when needed to assess lytic bone lesions.

Complete response (CR): Resolution of the baseline symptoms; no new bone lesions; normalization of the laboratory test results: complete blood cell (CBC) count, serum calcium, urinary protein, protein electrophoresis and immunofixation electrophoresis; normal myelogram and bone marrow biopsy.

Very good partial response (VGPR): Criteria as for MR, except: more than 90% decrease in serum monoclonal protein peak, more than 95% decrease in Bence Jones (BJ) protein excretion and bone marrow plasmacytosis < 5%.

Partial response (PR): Criteria as for MR, except: more than 50% decrease in serum monoclonal protein peak and at least 75% decrease in BJ protein excretion.

Minimal response (MR): No new lytic bone lesion(s) or enlargement of existing lesion(s) or other symptom(s)'; decrease in bone pain; normalization of hypercalcaemia; more than 20% but less than 50% decrease in the serum monoclonal protein peak or BJ protein excretion.

Stable disease (SD): At any time during the course of the disease, patients were considered stable if their disease did not meet the criteria for response or progressive disease.

Patients meeting any of the following criteria at anytime during the disease course were considered to have progressed. Progressive disease (PD) was defined as: increase in WHO performance status (by at least 1 point if baseline status was ≥1); extension of the myelomatous bone lesions; emergence, persistence or exacerbation of anaemia of central origin (with Hb < 80 g/l) or other signs of bone marrow insufficiency after having discounted an iatrogenic aetiology; emergence or exacerbation of kidney failure; emergence or exacerbation of hypercalcaemia (corrected serum calcium > 106 mg/l or 2.65 mmol/l); increase, confirmed by 2 successive assessments, of the monoclonal protein component. Depending on the baseline, a significant increase was to be considered as 30% or 5 g/l (50% increase of BJ protein). The relevant laboratory and bone radiological assessments performed at baseline were to be repeated to confirm disease progression.

Survival after progression was measured and defined as the time from first progression to death from any cause. This time was equal to 0 if progression and death occurred at the same date. Patients were censored at the last date that the patient was known to be alive, or at the data cut-off date (08 October 2005), whichever occurred first.

Sample size

Assuming a median survival time of 30 months in the control arm (MP), and using the Bonferroni correction for a global type I error rate of 5% in the two primary comparisons of the study (comparison of the MPT or the MEL100 arm to the control arm), sample size was estimated to be 500 in order to ensure a power of at least 80% in a two-sided test to detect an increase in the median survival time of 18 months (with an accrual time of 3 years and additional follow-up of 2 years). This clinically meaningful increase in median survival was considered plausible for each of the two treatments, MPT and MEL100, compared to MP and corresponds to an HR of 0.625 for death when comparing MPT or MEL100 to MP (about 101 deaths required in the two compared groups). Power calculations were not performed for each interim analysis, since the corresponding tests were performed with a type I error of 0.001, following the Peto-Haybittle rule [35].

Randomisation

Central randomisation to arms A, B and C in a ratio of 3:2:2 was done. No stratification was used.

Blinding (masking)

This was an open label study. Due to the nature and administration methods of the different treatments in this study, blinding was not feasible.

Statistical methods

All efficacy evaluations were conducted using the ITT population, except for supportive analysis of the primary endpoint and for best responses based on the PP population. Statistical comparison of efficacy findings was made between MP and MPT, MP and MEL100, and MPT and MEL100. The primary analysis involved comparisons between MP and MPT, and between MP and MEL100. Comparisons between MPT and MEL100 were performed as secondary analyses.

Time-to-event endpoints (death [OS], progression or death [PFS] and survival after progression) were analyzed using Kaplan-Meier (KM) survival methods from randomisation, or from progression for survival after progression. The number and percentage of events and censored observations were presented by treatment group and overall. Time-to-events were expressed as median +/- standard error (SE). The median time-to-event data were presented with 95% confidence limits. Additionally, univariate summary statistics (mean, standard deviation, minimum and maximum) for event times, unadjusted for censoring, were presented by treatment and overall. Differences in the survival distributions among treatment groups were assessed using two-sided unstratified log rank tests with α=0.025 level of significance. The hazard rate ratio and the corresponding 97.5% confidence interval were estimated using an unstratified Cox proportional hazards model. Overall survival comparisons between treatment groups were performed adjusting for prognostic factors through the proportional hazards model.

Baseline characteristics were analyzed for their prognostic value on OS from randomization, adjusted for treatment group, through a multivariate proportional hazards model, using forward selection with likelihood ratio test. In these prognostic analyses, each continuous variable was first divided into 5 categories at approximately the 20^{th}, 40^{th}, 60^{th}, and 80^{th} percentiles. After univariate analysis, all variables with a p-value less than 0.20 were subjected to multivariate analyses in several steps, first including all variables with no missing values and then successively including variables with an increasing number of missing values. At each step, the stability of the previously derived model was checked and no further analysis was performed in the case of instability. The proportional hazards assumption was checked for each prognostic factor included in the final model by testing a time (logarithm) by factor interaction term in the model. These analyses were performed in the ITT population.

RESULTS

Participant flow and recruitment

A total of 447 patients were randomized to one of the three treatment groups and comprised the ITT population. Enrolment began on 22 May 2000. The data cut-off for the analyses presented in the report was 8 October 2005. An update to OS was conducted for the IFM 99-06 study based on data collected through the cut-off date of 08 January 2007. Thus approximately 15 months of additional follow-up data has been obtained.

Before treatment initiation, 4 patients (3 and 1 randomized to MP and MPT, respectively) died and 4 patients randomized to MEL100 discontinued the study. Of the 447 patients who were randomized, 439 (98.2%) received at least one dose of study medication and comprised the safety population. A total of 427 (95.5%) patients, who had no major protocol deviations and took at least one dose of study medication, comprised the PP population.

The numbers of patients in the ITT population who were randomized to the MP, MPT and MEL100 treatment groups were 196 (43.8%), 125 (28.0%) and 126 (28.2%), respectively.

Approximately half of the patients who received MP or MPT received at least 9 cycles of MP. Of the 125 patients in the MPT group, 78 (62%) discontinued thalidomide prematurely and 47 (38%) had their initial dose reduced. A patient could have had a dose reduction and subsequently discontinue treatment. In the MEL100 group, 79 (65%) patients received the 2 planned transplants.

Two interim analyses were planned to take place after the inclusion of 200 (40%) and 350 (70%) patients. The minimum follow-up available for patients who were included in these analyses was 6 months at the first interim analysis and 5 months at the second. The first interim analysis took place as planned after the inclusion of 200 subjects on 02 January 2003. This first interim analysis found that there was no statistical advantage of one treatment over another. At the second interim analysis, which was performed in July 2004 and was 5 months after the enrolment of the 340^{th} patient, the DSMB recommended that recruitment should continue, but that a third interim analysis should be performed in May 2005. The third interim analysis was performed using all data available at that time (01 May 2005; 436 patients), and for 408 patients with a minimum follow-up of 5 months. Following the results of the third interim analysis, recruitment into the trial was stopped (on 08 August 2005, after the inclusion of 447 patients) due to a log rank p-value of 0.0008 in favour of MPT when OS was compared with that in the MP treatment group in the ITT population.

The additional follow-up time provided approximately 30% more deaths 268 compared to 206 in the analysis presented in the CSR and an increase in median follow-up time of approximately 40% (51.5 months compared to 36.8 months).

Patients who were alive at the time of analysis or who were lost to follow-up before death was documented were censored at the last date they were known to be alive. All censored information corresponded to administrative censoring, except for 1 MP-treated patient who was lost to follow-up approximately 20 months after randomization. The first censored observation for each treatment group occurred approximately 17 months after randomization.

Conduct of the study
There were twenty-two protocol amendments to the study, the majority of which related to modifications of the investigator list and/or extension of the study period.

Baseline data
Baseline demographic parameters were evenly distributed in the three treatment arms of the pivotal study (see table 12). This was true for baseline disease characteristics as well (data not shown). The impact of prognostic factors on primary outcome data is taken care of by the multivariate analyses conducted.

Table 12: Demographic characteristics – ITT population (study IFM 99-06)

Demographic Characteristic	MP (N=196)	MPT (N=125)	MEL100 (N=126)	Overall (N=447)
Age (Years)				
N	196	125	126	447
Mean ± Std Dev	69.7 ± 2.7	69.7 ± 2.9	69.4 ± 3.0	69.6 ± 2.8
Median	69.5	69.2	69.0	69.3
Min, Max	65, 75	64, 76	64, 82	64, 82
Age Group (Years) – n (%)				
< 70	112 (57.1)	75 (60.0)	77 (61.1)	264 (59.1)
≥ 70	84 (42.9)	50 (40.0)	49 (38.9)	183 (40.9)
Gender – n (%)				
Male	109 (55.6)	63 (50.4)	66 (52.4)	238 (53.2)
Female	87 (44.4)	62 (49.6)	60 (47.6)	209 (46.8)
Race – n (%)				
Caucasian	194 (99.0)	124 (100.0)	125 (99.2)	443 (99.3)
Other	2 (1.0)	0 (0.0)	1 (0.8)	3 (0.7)
Missing	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.2)

Abbreviations: ITT=intent-to-treat; Max=maximum; MEL100=melphalan 100 mg/m²; Min=minimum; MP=melphalan-prednisone; MPT=melphalan-prednisone plus thalidomide; Std Dev=standard deviation

Table 13: Second-line treatments in patients treated as assigned – safety population (study IFM 99-06)

	Number (%) of Patients		
Treatment	**MP (N=193)**	**MPT (N=124)**	**MEL100 (N=122)**
Not withdrawn	42	31	30
No second-line treatment received			
until death	24	11	18
still alive	1	27	1
Thalidomide alone or in combination	55	10	39
VAD [a]	42	15	1
Dexamethasone	12	7	1
Alkylating agent-based regimens	13	14	29
Bortezomib	3	7	3
Others	1	2	0

[a] Followed by transplantation in 9 patients in MP, and 3 patients in MPT

Outcomes and estimation

Primary efficacy endpoint

MPT treatment was superior to both MP and MEL100 for prolonging OS, with the median survival increased by 21.4 and 15.0 months, respectively. The primary comparison (MPT:MP) for the primary endpoint of OS showed MPT to be superior to MP (HR 0.56, 97.5% CI 0.37 to 0.84, p=0.0012). The

secondary comparison (MPT:MEL100), was associated with an OS advantage for MPT compared with MEL100 (HR 0.58, 97.5% CI 0.37 to 0.89, p=0.0048).

After approximately 15 months of additional follow-up survival data, the median OS advantage was 18.4 months for MPT relative to MP treatment. The updated OS data had an observed hazard ratio of MPT to MP of 0.59 (97.5% CI 0.42 to 0.84) compared to the corresponding hazard ratio in the clinical study report of 0.56 (97.5% CI 0.37 to 0.84).

The numbers (percentage) of patients who died up to the data cut-off date of 08 January 2007 were 62 (49.6%), 128 (65.3%), and 78 (61.9%), in the MPT (n=125), MP (n=196) and MEL100 groups (n=126), respectively. Median OS times were 51.6, 33.2, and 38.3 months in the MPT, MP and MEL100 groups, respectively. The MPT survival curve separated from the MP and MEL100 curves at about 2 months and remained separated for the duration of the study.

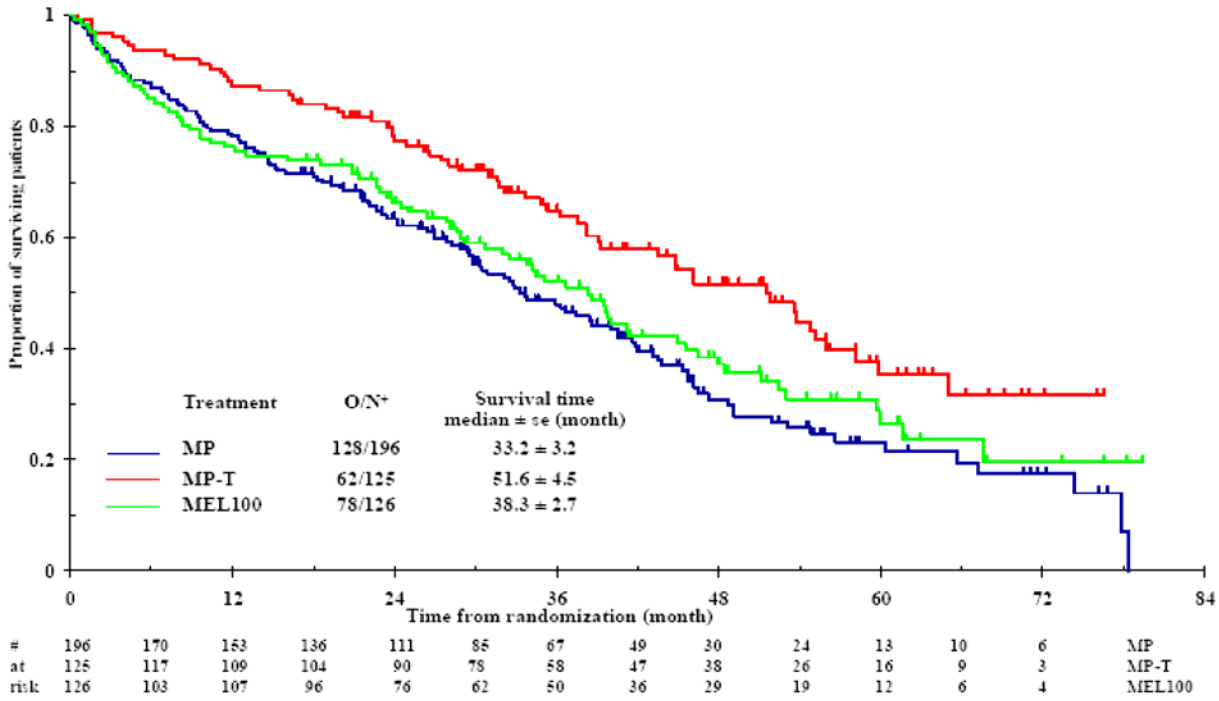
Table 14: Summary of overall survival – ITT population (study IFM 99-06)

Overall Survival	**MP (N=196)**	**MPT (N=125)**	**MEL100 (N=126)**
Died – n (%)	128 (65.3)	62 (49.6)	78 (61.9)
Censored – n (%)	68 (34.7)	63 (50.4)	48 (38.1)
Follow-up (Months)			
Median	46.9	51.3	51.6
95% CI	38.5, 55.4	43.8, 58.7	43.2, 59.9
OS Time (Months)			
Median	33.2	51.6	38.3
95% CI	27.0, 39.4	42.7, 60.4	32.9, 43.7
Hazard Ratio (97.5% CI) [b, c]	1	0.59 (0.42, 0.84)	-
P-value [a, c]		0.0008	-
Hazard Ratio (97.5% CI) [b, d]	-	0.69 (0.47, 1.00)	1
P-value [a, d]	-		0.0215

[a] Based on a two-sided unstratified log rank test of survival curve differences between treatment groups; [b] Based on a proportional hazards model comparing the hazard functions associated with treatment groups (MP:MPT and MP:MEL100); [c] MPT:MP comparison; [d] MPT:MEL100 comparison.

A Kaplan-Meier estimate of the survival curve by treatment group for the ITT population is presented in Figure 1.

Figure 1. Updated overall survival – ITT population (study IFM -99-06)



Abbreviations**:** ITT-intent to treat; MEL100=melphalan 100 mg/m^2; MP=melphalan-prednisone; MPT=melphalan-prednisone plus thalidomide; N=number of patients at randomisation; O=number of deaths; se=standard error. **Notes:** This summary excludes any observation that occurred after 8 January 2007.

Table 15: Prognostic factors of overall survival – ITT population (study IFM 99-06)

Factor	Category		Hazard Ratio		p-value
	Reference	Risk	Estimate	95% CI	
Factor					
WHO index	0-1	2	1.3	0.9, 1.9	0.010
		3-4	2.1	1.3, 3.3	
ß2-microglobulin level (mg/L)	< 2.5	≥ 2.5	1.8	1.1, 2.9	0.015
Albumin level (g/dL)	≥ 3.5	< 3.5	1.6	1.2, 2.2	0.005
Hemoglobin level (g/dL)	> 9	≤ 9	1.8	1.3, 2.5	<0.001
White blood cell count (10^9/L)	≤ 6	> 6	1.5	1.1, 2.0	0.011
Bone marrow plasmacytosis (%)	≤ 60	> 60	1.5	1.1, 2.3	0.032
Treatment comparison					
Primary comparisons	MP	MPT	0.49	0.33, 0.73	0.0002
	MP	MEL100	0.88	0.62, 1.24	0.46
Secondary comparisons	MEL100	MPT	0.56	0.37, 0.85	0.006

Response results	MP (N=196)	MPT (N=125)	MEL100 (N=126)
Overall response – n (%)	153 (78.1)	107 (85.6)	105 (83.3)
CR – n (%)	5 (3.3)	16 (15.0)	20 (19.0)
VGPR – n (%)	10 (6.5)	30 (28.0)	31 (29.5)
PR – n (%)	63 (41.2)	45 (42.1)	36 (34.3)
Response (CR+VGPR+PR) – n (%)	78 (51.0)	91 (85.0)	87 (82.9)

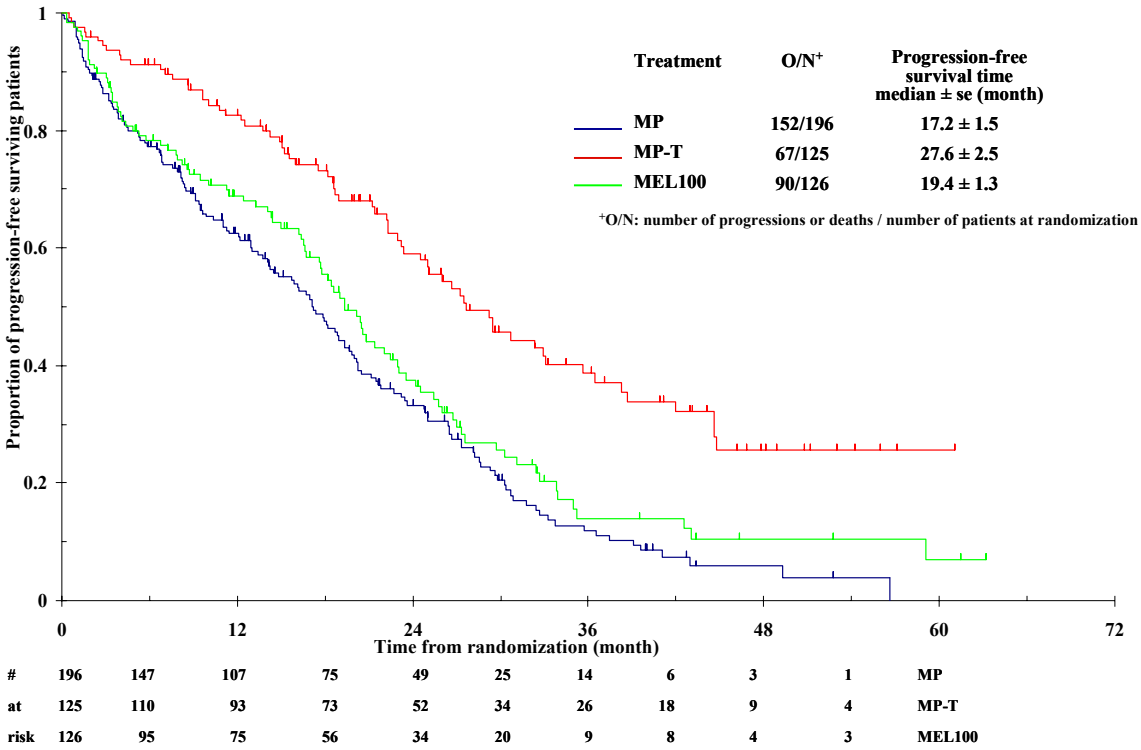
Secondary efficacy endpoint

Patients in the MPT group had a 55% (HR 0.45, 97.5% CI 0.32 to 0.62, p<0.0001) and 46% (HR 0.54, 97.5% CI 0.38 to 0.78, p=0.0001) reduced risk of disease progression or death compared to subjects in the MP and MEL100 groups, respectively. For the ITT population, the PFS rate was higher in the MPT group than in the MP and MEL100 groups at 1, 2, and 3 years.

Table 16: Summary of progression free survival – ITT population (study IFM 99-06)

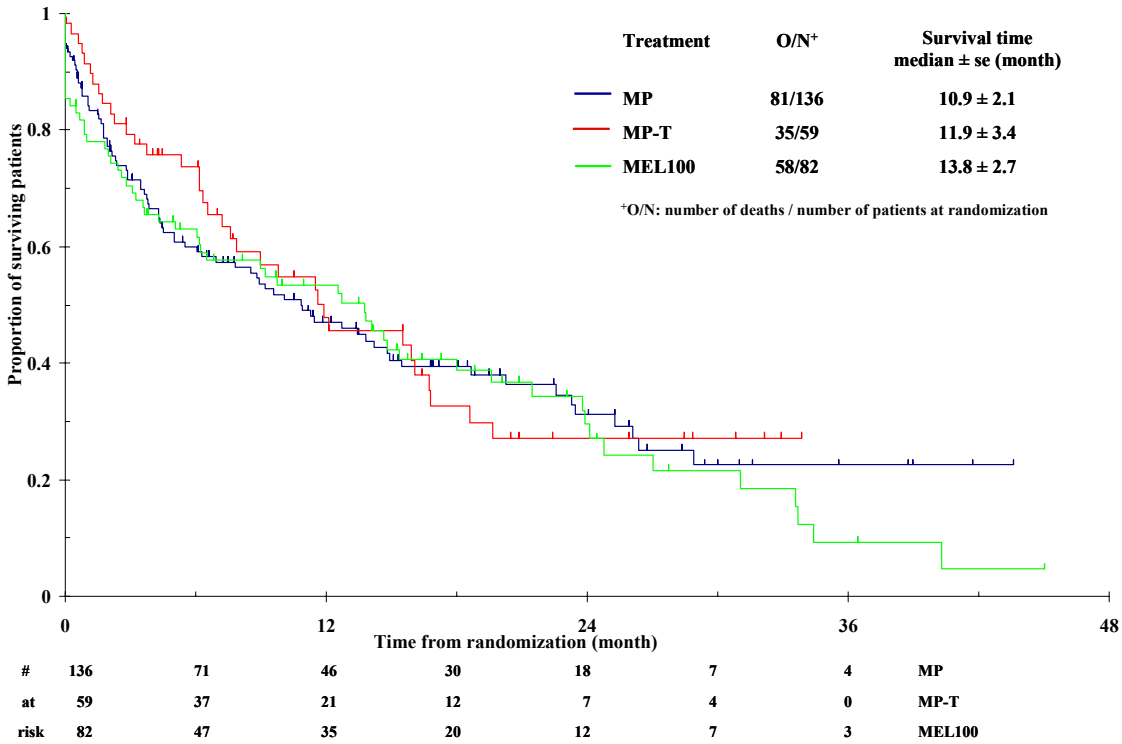
Progression Free Survival (PFS)	**MP (N=196)**	**MPT (N=125)**	**MEL 100 (N=126)**
Progressed or died– n (%)	152 (77.6)	67 (53.63)	90 (71.4)
Censored – n (%)	44 (22.4)	58 (46.4)	36 (28.6)
Overall PFS time (months)			
Median	17.2	27.6	19.4
95% CI	14.3, 20.2	22.6, 32.6	16.9, 21.9
Hazard Ratio (97.5% CI) [b, c]	1	0.45 (0.32, 0.62)	-
P-value [a, c]		<0.0001	-
Hazard Ratio (97.5% CI) [b, d]	-	0.54 (0.38, 0.78)	1
P-value [a, d]	-	0.0001	
Hazard Ratio (97.5% CI) [b, e]	1	-	0.82 (0.61, 1.11)
P-value [a, e]		-	0.1371

Figure 2: Progression free survival – ITT population (study IFM 99-06)



A conservative sensitivity analysis correcting for asymmetrical visit schedules demonstrated results that were consistent with the main PFS analysis. Specifically, actual censoring and event times for the MPT-treated patients were reassigned to the earlier scheduled assessment times and were analyzed in the same way as the main PFS analysis. These results showed a statistically significant prolongation of PFS for patients treated with MPT compared with MP and MEL100 (log rank p-values of <0.001 and 0.0012, respectively; median time to PFS was 24 months for MPT; median times to PFS remained the same for MP and MEL100).

Figure 3: Survival after progression – ITT population (study IFM 99-06)



Ancillary analyses

The median survival after progression times in the entire ITT population in the MPT (11.9 months) and MP (10.9 months) groups were identical to those obtained in the subset of patients who progressed. These results may provide some evidence that the primary endpoint of OS was not affected by treatment after progression. However, this study was not powered to assess this question so these results should be interpreted with caution and no definitive conclusions drawn.

The OS data was consistent regardless of subgroup based on selected prognostic factors (see table 17). The beneficial effect was even more pronounced in most unfavourable groups of patients, e.g. those with performance status 2, ß2-M ≥ 2.5, DS stage III and chromosomal aberration. One unfavourable (small) group that was not gaining benefit from the addition of thalidomide to MP was patients with elevated creatinine, serum creatinine ≥ 20.

Table 17: Median survival time and interaction with treatment group – ITT Population

Median Survival Time ± SE (Months)	MP (N=196)	MPT (N=125)	MEL100 (N=126)
ISS Stage			
Patients with ISS stage 1 (O/N)	40.6 ± 6.2 (23/61)	53.6 ± 4.6 (11/38)	45.6 ± 6.7 (12/33)
Patients with ISS stage 2 (O/N)	38.5 ± 9.1 (31/67)	51.6 ± 6.2 (18/42)	45.0 ± 8.2 (20/42)
Patients with ISS stage 3 (O/N)	26.9 ± 5.1 (34/54)	NE (10/32)	26.4 ± 7.7 (28/41)
Chromosome 13 Deletion			
Patients with deletion (O/N)	27.8 ± 6.1 (48/77)	44.8 ± 6.9 (17/49)	32.0 ± 8.0 (29/46)
Patients without deletion (O/N)	32.2 ± 5.9 (30/70)	54.8 ± 2.4 (17/52)	41.4 ± 6.9 (25/55)
Durie-Salmon (DS) Stage			
Patients with DS stage I (O/N)	30.3 ± NE (6/18)	35.3 ± 6.3 (4/13)	NE (1/7)
Patients with DS stage II (O/N)	43.6 ± 4.4 (21/50)	54.8 ± 7.5 (9/33)	45.0 ± 3.5 (8/22)
Patients with DS stage III (O/N)	28.2 ± 2.9 (70/127)	53.6 ± 7.1 (30/79)	32.0 ± 4.2 (57/97)
WHO Performance Status			
Patients with a WHO status of 0-1 (O/N)	40.6 ± 4.6 (66/149)	51.6 ± 4.9 (30/87)	41.4 ± 3.4 (37/79)
Patients with a WHO status of 2 (O/N)	26.9 ± 7.9 (20/33)	NE (7/28)	29.1 ± 7.0 (18/33)
Patients with a WHO status of 3-4 (O/N)	14.7 ± 3.5 (10/13)	16.1 ± 10.6 (6/10)	9.5 ± 8.9 (11/14)
Serum β2-Microglobulin (mg/L)			
Patients with ß2-M < 2.5 (O/N)	53.1 ± 11.8 (7/33)	53.8 ± 7.7 (5/20)	45.6 ± 8.0 (6/17)
Patients with ß2-M ≥ 2.5 (O/N)	29.8 ± 4.3 (81/149)	51.6 ± 7.0 (34/92)	35.2 ± 4.9 (55/100)
Serum Creatinine (mg/L)			
Patients with serum creatinine < 20 (O/N)	32.2 ± 4.2 (90/183)	53.8 ± 1.7 (35/113)	40.1 ± 4.9 (52/109)
Patients with serum creatinine ≥ 20 (O/N)	21.6 ± 8.5 (7/13)	16.1 ± 15.7 (7/11)	18.6 ± 9.2 (14/17)
Translocation t_{4-14} of chromosome 14			
For patients without translocation (O/N)	32.2 ± 6.7 (47/88)	53.6 ± 6.4 (18/47)	40.1 ± 4.8 (32/63)
For patients with translocation (O/N)	12.5 ± 3.1 (6/7)	20.3 ± 8.9 (5/10)	38.6 ± 19.4 (5/7)
Translocation t_{11-14} of chromosome 14			
For patients without translocation (O/N)	27.0 ± 3.9 (50/84)	44.8 ± 11.2 (20/47)	40.1 ± 4.4 (30/55)
For patients with translocation (O/N)	43.6 ± 11.5 (3/11)	NE (3/11)	32.5 ± 6.9 (7/15)
Bone Lesions			
Patients with no bone lesion (O/N)	42.0 ± NE (14/40)	35.3 ± 10.3 (11/29)	33.9 ± 4.6 (11/23)
Patients with at least 1 bone lesion (O/N)	30.9 ± 4.4 (82/154)	54.8 ± NE (30/90)	39.5 ± 3.2 (53/99)

Abbreviations: DS=Durie-Salmon; ISS= international staging system; MEL100=melphalan 100 mg/m²; MP=melphalan-prednisone; MPT=melphalan-prednisone plus thalidomide; NE=not estimable; O/N=number of deaths/number of patients at randomization; SE=standard error; WHO=World Health Organization; Δ 13=deletion of chromosome 13; ß2-M=beta2-microglobulin.

- Analysis performed across trials (pooled analyses and meta-analysis)

There was no analysis performed across trials.

- Clinical studies in special populations

There was no analysis performed in special populations.

- Supportive studies

GISMM2001

METHODS

The GISMM2001 study was a randomized, open-label, controlled, multicenter study comparing thalidomide in combination with MP *versus* MP alone in patients who were older than 65 years of age (or younger patients unable to undergo transplantation) with newly diagnosed multiple myeloma.

Patients in the MPT arm received thalidomide 100 mg/day orally with melphalan at 4 mg/m^2 on Days 1 to 7 and prednisone at 40 mg/m^2 on Days 1 to 7. Patients in the MP arm received melphalan and prednisone at the same dose and schedule used in the MPT arm. This cycle was repeated every 4 weeks for a standard 6 cycles. After completion of the 6 cycles thalidomide could be administered at 100 mg/day as maintenance therapy until progression.

The primary objectives of this study were to compare clinical response rates and event free survival (EFS) between treatment groups. The secondary efficacy endpoints included OS, prognostic factors, and time to first response. EFS was calculated as the time from the diagnosis to progression/ relapse, death of any cause, or the date the patient was last known to be in remission.

Response to treatment was monitored by measurement of myeloma protein in serum and urine every 4 weeks. Response rate was assessed by the local investigator, according to the Bladé response criteria at 6 months (i.e. after the 6 cycles of MP/MPT).

Two interim analyses were performed during the study. The first interim analysis was done for safety monitoring. At the second interim analysis (data lock 15 June 2005) the study was stopped (87% of planned recruitment) and 255 patients with at least 6 months follow-up were included in the analysis (minimal time required to evaluate clinical response).

RESULTS

The baseline demographics and disease characteristics were balanced between the treatment groups. The median age of study participants was 72 (range 60-85) years.

The second interim analysis showed the MPT group as having a significant improvement in the response rate ($p<0.0001$) and EFS ($p=0.0006$) compared with the MP group. Treatment with MPT produced a higher response rate (complete response + partial response) 76.0% compared to a 47.6% response rate in the MP treatment group. The 2-year event free survival rates were significantly longer in the MPT treatment group (54%) compared with the MP treatment group (27%) (HR 0.51, 95% CI 0.35-0.75, p=0.0006).

Table 18: Response Rate (study GISMM2001)

	Treatment		Absolute Difference
	MPT (N=129)	**MP (N=126)**	**MPT – MP (95% CI)**
Number of Responders (CR+PR) – n (%)	98 (76.0)	60 (47.6)	28.3% (16.5 to 39.1)
Complete Response (CR) – n (%)	20 (15.5)	3 (2.4)	13.1% (6.3 to 20.5)
Partial Response (PR) – n (%)	78 (60.4)	57 (45.2)	15.2% (3.0 to 26.9)
Minimal Response (MR) – n (%)	7 (5.4)	21 (16.7)	-11.2% (-19.2 to -3.6)
No Response (NR) – n (%)	7 (5.4)	19 (15.1)	-9.7% (-17.4 to -2.2)
Progressive Disease (PD) – n (%)	10 (7.8)	21 (16.7)	-8.9% (-17.2 to -0.8)
Not Evaluable (NE) – n (%)	7 (5.4)	5 (4.0)	--

THAL-MM-003

METHODS

This was a multicenter, randomized, parallel-group, double blind, placebo controlled study of combination thalidomide plus dexamethasone therapy *versus* dexamethasone therapy alone as induction therapy for previously untreated patients with multiple myeloma. The main inclusion criteria were patient ≥ 18 years; diagnosis of active multiple myeloma (Durie-Salmon Stage II and III; and must not have received previous anti-myeloma systemic therapy (previous local radiotherapy was permissible). Radiation therapy initiated prior to baseline (Day 1) could have been given in conjunction with study drug, provided that all other eligibility criteria were satisfied; Measurable levels of myeloma paraprotein in serum (≥ 1.0 g/dL) or urine (≥ 0.2 g excreted in a 24-hour collection sample); ECOG performance status score of 0, 1, or 2. The primary efficacy endpoint was time to disease progression (TTP), defined as the number of days from randomization to the first documentation of disease progression, as determined by the RRC, based on the Bladé myeloma response criteria. Secondary efficacy endpoints was PFS (defined as the time from randomization to documented progression, as determined by the RRC, or death from any cause, whichever occurred first), myeloma response rate (based on the best response assessment during the treatment period, as determined by the RRC, and categorized according to the Bladé myeloma response criteria), complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), duration of myeloma response, time to first symptomatic skeletal-related event and overall survival.

RESULTS

Baseline data

Table 19: Demographic characteristics - ITT population (study THAL-MM-003)

Demographic Characteristic	Thalidomide / Dexamethasone (N=235)	Placebo / Dexamethasone (N=235)	Overall Total (N=470)
Age (Years)			
N	235	235	470
Mean ± Std Dev	64.0 ± 10.17	64.4 ± 9.57	64.2 ± 9.86
Median	65.0	66.0	65.0
Min, Max	39, 86	31, 84	31, 86
Gender – n (%)			
Male	118 (50.2)	120 (51.1)	238 (50.6)
Female	117 (49.8)	115 (48.9)	232 (49.4)
Height (cm)			
N	232	223	455
Mean ± Std Dev	166.3 ± 9.69	166.1 ± 9.77	166.2 ± 9.72
Median	165.1	165.0	165.0
Min, Max	135.0, 191.0	144.0, 205.9	135.0, 205.9
Weight (kg)			
N	235	233	468
Mean ± Std Dev	73.3 ± 15.55	74.0 ± 15.73	73.6 ± 15.63
Median	72.0	72.0	72.0
Min, Max	46.0, 150.0	42.3, 142.9	42.3, 150.0
BMI (kg/m^2)			
N	232	223	455
Mean ± Std Dev	26.4 ± 4.64	26.4 ± 4.38	26.4 ± 4.51
Median	25.6	26.0	25.7
Min, Max	17.4, 48.1	17.1, 40.8	17.1, 48.1

Table 20: Disease characteristics - ITT Population (study THAL-MM-003)

Disease Characteristic	Thalidomide / Dexamethasone (N=235)	Placebo / Dexamethasone (N=235)	Overall Total (N=470)
Time from First Diagnosis of Active MM (Weeks) [a]			
N	235	235	470
Mean ± Std Dev	14.1 ± 40.13	11.9 ± 28.15	13.0 ± 34.64
Median	4.3	4.4	4.3
Min, Max	0.0, 372.7	0.0, 185.6	0.0, 372.7
Baseline MM Stage (Durie-Salmon) – n (%)			
I	2 (0.9)	2 (0.9)	4 (0.9)
II	76 (32.3)	88 (37.4)	164 (34.9)
III	157 (66.8)	145 (61.7)	302 (64.3)
ECOG Performance Status – n (%)			
0	40 (17.0)	54 (23.0)	94 (20.0)
1	124 (52.8)	112 (47.7)	236 (50.2)
2	70 (29.8)	68 (28.9)	138 (29.4)
3	0 (0.0)	1 (0.4)	1 (0.2)
Missing	1 (0.4)	0 (0.0)	1 (0.2)
Lytic Bone Lesions – n (%)			
Present	185 (78.7)	188 (80.0)	373 (79.4)
Absent	49 (20.9)	46 (19.6)	95 (20.2)
Missing	1 (0.4)	1 (0.4)	2 (0.4)
Bone Marrow Apirate/Biopsy Cellularity – n (%)			
Normal	102 (43.4)	108 (46.0)	210 (44.7)
Hyperplasia	77 (32.8)	76 (32.3)	153 (32.6)
Hypoplasia	53 (22.6)	50 (21.3)	103 (21.9)
Missing	3 (1.3)	1 (0.4)	4 (0.9)
Plasma Cells (%)			
N	231	233	464
Mean ± Std Dev	39.3 ± 24.69	38.9 ± 23.91	39.1 ± 24.28
Median	36.0	35.0	35.0
Min, Max	0.0, 100.0	2.0, 100.0	0.0, 100.0
Prior Radiotherapy – n (%)			
Yes	28 (11.9)	29 (12.3)	57 (12.1)
No	207 (88.1)	206 (87.7)	413 (87.9)
Baseline Beta-2 Microglobulin – n (%)			
≤ 2.5 mg/L	33 (14.0)	35 (14.9)	68 (14.5)

Disease Characteristic	Thalidomide / Dexamethasone (N=235)	Placebo / Dexamethasone (N=235)	Overall Total (N=470)
> 2.5 mg/L	200 (85.1)	199 (84.7)	399 (84.9)
Missing	2 (0.9)	1 (0.4)	3 (0.6)
ECG [b] – n (%)			
Normal	70 (29.8)	95 (40.4)	165 (35.1)
Abnormal			
NCS	135 (57.4)	112 (47.7)	247 (52.6)
CS	23 (9.8)	24 (10.2)	47 (10.0)
Missing	7 (3.0)	4 (1.7)	11 (2.3)

Outcomes and estimation

Table 21: Summary of time to progression - ITT population (study THAL-MM-003)

	Thalidomide / Dexamethasone (N=235)	Placebo / Dexamethasone (N=235)
Time to Progression		
Progressed – n (%)	72 (30.6)	126 (53.6)
Censored – n (%)	163 (69.4)	109 (46.4)
Overall Time to Progression (Weeks)		
Median	97.7	28.3
95% CI [a]	61.86, NE	27.71, 36.43
Hazard Ratio (95% CI) [b]	0.43 (0.32, 0.58)	
P-value [c]	<0.0001	
P-value [d]	<0.0001	

E1A00

METHODS

This study was a randomized, multicenter, open label, controlled, parallel group phase 3 trial in patients with newly diagnosed multiple myeloma conducted by the ECOG study group. Patients were randomized to thalidomide/dexamethasone or dexamethasone alone. Patients randomized to the thalidomide/dexamethasone treatment group received thalidomide 200 mg orally once daily for 28 days (1 treatment cycle) plus dexamethasone 40 mg orally once daily on days 1-4, 9-12, and 17-20 for the 28-day treatment cycle. Patients randomized to dexamethasone alone treatment group received dexamethasone 40 mg orally once daily on days 1-4, 9-12, and 17-20 of the 28-day treatment cycle. These treatment regimens were repeated every 4 weeks for a total of 4 cycles. Following 4 treatment cycles, eligible patients that had not progressed were eligible to receive stem cell transplantation. Patients who had not progressed and were not eligible for stem cell transplant received either standard MM therapy or continued on thalidomide and/or dexamethasone in an extension phase at the investigator's discretion until progression.

RESULTS

The baseline demographics and disease characteristics were in general well balanced between the treatment groups. The median age of study participants was 64 (range 38-83) years.

Table 22: Best response rate for first 4 cycles - efficacy population (study E1A00)

ECOG Criteria	Thalidomide / Dexamethasone (N=99)	Dexamethasone Only (N=101)	p-value
Number of Responders (CR+NCR+PR) - n (%)	61 (61.6)	40 (39.6)	0.001 [a]
Complete Response (CR) – n (%)	5 (5.1)	0	
Near Complete Response (NCR) – n (%)	0	1(1.0)	
Partial Response (PR) – n (%)	56 (56.6)	39 (38.6)	
No Change (NC) or Stable Disease (SD) – n (%)	21 (21.2)	38 (37.6)	
Progressive Disease (PD) – n (%)	2 (2.0)	3 (3.0)	
Not Evaluable (NE) – n (%)	15 (15.2)	20 (19.8)	

Based on ECOG criteria, the time to the best myeloma response during the first 4 cycles of treatment was similar between treatment groups with a median time of 4.9 weeks for patients in the thalidomide/dexamethasone treatment group compared to 5.1 weeks for patients in the dexamethasone only treatment group. The time to first confirmed response was also similar with a median of 4.9 weeks in both treatment groups.

- Discussion on clinical efficacy

No dose response studies with thalidomide were conducted by the applicant. The lack of phase II study is justified by narrow safety margin (100mg - 400mg). When considering patient year of exposure in the IFM 99-06 study, there were no adverse events that appeared to be dose related within the range of doses (50 to 400 mg). However, a greater percentage of patients who received a maximum dose of 400 mg/day required subsequent dose reductions than those who received a maximum daily dose of 200mg/day indicating that patient tolerability was better at the 200 mg/day dose. Based on this information, the CHMP has recommended that thalidomide is administered orally at 200 mg per day for a duration, as tolerated, of up to 12 cycles of 6 weeks (see SPC section 4.2).

In the pivotal study IFM 99-06 the melphalan-prednisone regimen was considered as a valid comparator, and a valid additive design due to the differing toxicity profiles between thalidomide and the agents used in the combination. The use of overall survival (OS) as primary efficacy endpoint is in line with CHMP guideline [36] and is particularly preferred in an open label design. However, with emerging new treatment options in multiple myeloma (MM), it is anticipated that the survival time is affected by later lines of treatment and progression free survival (PFS) may become more appropriate for the primary analysis. A secondary analysis of OS after disease progression addressed this issue.

The increased median OS time from 32.2 to 53.6 months when thalidomide is added to MP, comprising an additional 21.4 months was considered a substantial clinical benefit for the targeted patient population. The HR is 0.56 (0.37, 0.89) with p=0.0012. The efficacy of thalidomide in combination with MP when compared to MP alone tended to be higher in worst prognostic population (deletion q13, high serum β2- microglobulin level) and Durie-Salmon (DS) stages III patients. However, the IFM 99-06 study was not designed for prognostic factors sub-group analysis. The 15 months follow-up data showed that the OS advantage was maintained with updated median survival times of 51.6 ± 4.5 and 33.2 ± 3.2 months in the MPT and MP groups, respectively (HR 0.59, 97.5% CI 0.42 to 0.84).

Secondary efficacy measures were all in support of the primary analysis. Sensitivity analysis of PFS adjusting for differential delay of visits confirmed the initial analysis results. The response rates of MPT concerning CR and VGPR were as good as those obtained with the high dose regimen combined with ABMT. OS, however, was better with MPT, reflecting either treatment induced mortality with high dose chemotherapy or a superior efficacy of the thalidomide combination in early treatment of MM, at least in the population aged between 65 and 75.

MPT appeared superior to MEL100 (increase in median survival time of 15 months in MPT group over MEL100). However, only a few patients received the complete MEL 100 regimen making impossible the comparison between MEL100 and MPT.

The 41/16/21 % of patients withdrawn in the MPT/MP/MEL100 arms did not receive second line treatment. So the OS outcome was obtained despite less treatment after withdrawal from study treatment, irrespective of cause, of the patients in the thalidomide treated group. The type of second-line treatment differed as expected considerably between treatment arms. Nine patients in the MP arm and 3 patients in the MPT arm received VAD followed by transplantation. The survival after progression was very similar irrespective of treatment assignment, indicating that the primary endpoint OS was not affected by treatment after progression, and supporting the first line indication for thalidomide.

The GISMM2001 study is supporting the conclusion drawn from the pivotal IFM 00-07 study that the addition of thalidomide to MP is enhancing the anti-myeloma effect of the chemotherapy. This is shown by the increased ORR, the prolongation of EFS and trend of increased OS. The regimen given in this study was more toxic, as the proportion of early deaths was increased in the experimental arm.

The pivotal company-sponsored trial THAL-MM-003 (and the supportive E1A00 study) conducted by the Eastern Cooperative Oncology Group investigated thalidomide plus dexamethasone therapy *versus* dexamethasone therapy alone as induction therapy for previously untreated subjects with multiple myeloma. The following limitations were identified:
- Dexamethasone alone is not the gold standard for induction especially in young MM patients. The right comparator should have been e.g. VAD in a large subset of included patients [6].
- The study (THAL-MM-003) population (age ≥ 18 years, MM Durie-Salmon stage II and III, not having received previous anti-myeloma systemic, ECOG performance status score of 0, 1, or 2) is not representative of the target population (18 to 65 years old, newly diagnosed MM patients eligible to HDT/ASCT).
- Neither TTP (THAL-MM-003) nor overall best response based (in E1A00) are appropriate primary endpoints to serve the objective i.e. achievement of successful transplantation.
This (induction) indication supported by these data was withdrawn by the applicant after the first list of questions.

Clinical safety

- Patient exposure

A total of 1260 patients/subjects involved in the clinical pharmacology and controlled clinical studies received a treatment. A total of 610 patients/subjects received thalidomide (see table 23).

Data from clinical studies (IFM 99-06, THAL-MM-003, and E1A00) were not pooled but analysed for each study as the criteria used to "grade" adverse events were different across these 3 controlled clinical studies. Safety data from studies GIMEMA and GISMM2001 were not presented.

In study IFM 99-06, the planned 12 cycles of MP were completed by a higher proportion of patients in the MP group than in the MPT group (36.7% vs. 25.8%, respectively). For the entire study (18 months), in the MPT group, the median duration of thalidomide treatment was 10.5 months, and the median daily dose was 217.4 mg.

In THAL-MM-003 study, treatment exposure ranged from 1 day to 28 weeks (6.5 months). Exposure was from 6.5 months up to a year for 18.8% and 19.2% of thalidomide and dexamethasone patients, respectively (thalidomide/dexamethasone combination), and 30.6% and 29.7% placebo and dexamethasone patients, respectively (placebo/dexamethasone combination). The median average daily dose overall was 200 mg for thalidomide or placebo associated in both groups with concomitant 40 mg dexamethasone.

Table 23: Overall extent of exposure to study drug

	Number of Subjects/Patients						
		First-Line Therapy			Induction Therapy		
Study	**thalidomide alone**	**Melphalan / Prednisone**	**Melphalan / Prednisone / Thalidomide**	**Intensive treatment**	**Thalidomide /dexamethasone**	**Dexamethasone**	**Total [a]**
P030130 / THA I EU 2004 BA 001	18	–	–	–	–	–	18
PK-001	17	–	–	–	–	–	17
PK-003	12[b]	–	–	–	–	–	12
PK-004	15	–	–	–	–	–	15
PK-006	13	–	–	–	–	–	13
PK-007	22	–	–	–	–	–	22
Thal-BA-001	18	–	–	–	–	–	18
Thal-PK-011	18[c]	–	–	–	–	–	18
Thal-PK-012	18[d]	–	–	–	–	–	18
			Controlled Clinical Studies				
IFM 99-06	–	193	124	122	–	–	439
THAL-MM-003	–	–	–	–	234	232[e]	466
E1A00	–	–	–	–	102	102	204
Total	***151***	***193***	***124***	***122***	***336***	***334***	***1260***

[a] Total of patients in all treatment groups; [b] Subjects were also dosed with Ortho-Novum 1/35. A total of 12 subjects were exposed to treatment during the study, 1 subject did not receive thalidomide but received Ortho-Novum 1/35; [c] Subjects were also dosed with digoxin 0.5 mg on Day 5 of thalidomide treatment; [d] Subjects were also dosed with warfarin 25 mg on Day 4 of thalidomide treatment; [e] Dexamethasone was in combination with placebo.

- Adverse events

Tables 24 and 25 shows the most frequently adverse events as observed from the pivotal studies IFM 99-06 and THAL-MM-03.

Table 24: Most frequently observed (> 7.5%) adverse events by preferred term (study IFM 99-06)

	Number (%) of Patients	
Preferred Term[a]	**MP Group (N=193)**	**MPT Group (N=124)**
Neutropenia	63 (32.6)	58 (46.8)
Leukopenia	32 (16.6)	35 (28.2)
Constipation	1 (0.5)	28 (22.6) *
Somnolence	0	28 (22.6) *
Anaemia	38 (19.7)	27 (21.8)
Paresthesia	4 (2.1)	23 (18.5) *
Peripheral neuropathy	0	21 (16.9) *
Lymphopenia	14 (7.3)	19 (15.3) *
Thrombocytopenia	23 (11.9)	15 (12.1)
Dizziness	5 (2.6)	15 (12.1) *
Peripheral edema	3 (1.6)	15 (12.1) *
Dysesthesia	1 (0.5)	15 (12.1) *
Neuropathy	0	15 (12.1) *
Tremor	0	14 (11.3) *
Asthenia	3 (1.6)	10 (8.1) *
Peripheral sensory neuropathy	1 (0.5)	10 (8.1) *

[a] Multiple occurrences of the same preferred term were counted only once per patient. Preferred terms were coded using MedDRA Version 9.0. * Incidence at least 2-fold greater than in the MP group (where the incidence in the MPT group was ≥ 1%). Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; WHO=World Health Organization Note: For the MP and MPT treatment groups, skin, neurological, cardiac, and thrombotic events of all WHO grades or intensities were reported. For all other adverse events, only those of WHO Grades ≥ 3 or of severe intensity were reported and only if, according to the investigator, they were not attributable to progression of the myeloma.

Table25: Most frequently observed (> 10%) adverse events by preferred term (THAL-MM-003)

Preferred Term[a]	Number (%) of Patients	
	Thalidomide/Dexamethasone (N=234)	Placebo/Dexamethasone (N=232)
Constipation	116 (49.6)*	49 (21.1)
Oedema peripheral	80 (34.2)	57 (24.6)
Tremor	62 (26.5)*	29 (12.5)
Asthenia	56 (23.9)	47 (20.3)
Dizziness	51 (21.8)	32 (13.8)
Fatigue	50 (21.4)	36 (15.5)
Headache	42 (17.9)	46 (19.8)
Insomnia	41 (17.5)	63 (27.2)
Anaemia NOS	38 (16.2)	30 (12.9)
Pyrexia	37 (15.8)	42 (18.1)
Hyperglycaemia NOS	36 (15.4)	32 (13.8)
Weight increased	35 (15.0)	42 (18.1)
Pneumonia NOS	35 (15.0)	28 (12.1)
Bone pain	33 (14.1)	36 (15.5)
Weight decreased	32 (13.7)	34 (14.7)
Muscle weakness NOS	32 (13.7)	31 (13.4)
Oedema NOS	31 (13.2)	19 (8.2)
Back pain	30 (12.8)	34 (14.7)
Nausea	30 (12.8)	27 (11.6)
Deep vein thrombosis	30 (12.8)*	4 (1.7)
Rash NOS	29 (12.4)	30 (12.9)
Cough	27 (11.5)	33 (14.2)
Anxiety	27 (11.5)	22 (9.5)
Upper respiratory tract infection NOS	27 (11.5)	22 (9.5)
Dyspepsia	27 (11.5)	21 (9.1)
Paraesthesia	27 (11.5)	15 (6.5)
Diarrhoea NOS	24 (10.3)	40 (17.2)
Depression	24 (10.3)	19 (8.2)
Peripheral sensory neuropathy	24 (10.3)	12 (5.2)
Arthralgia	22 (9.4)	35 (15.1)

* Incidence at least 2-fold greater than in the placebo/dexamethasone group; [a] Preferred terms are listed in descending order of frequency for the thalidomide/dexamethasone column. Multiple occurrences of the same preferred term are counted only once per patient. Preferred terms were coded using MedDRA Version 5.1. Abbreviation: MedDRA=Medical Dictionary for Regulatory Activities; NOS=not otherwise specified

Table 26: Summary of adverse events of special interest in studies IFM 99-06 and THAL-MM-003

	Number (%) of Patients			
	Study IFM 99-06		Study THAL-MM-003	
Category [a]	MPT (N=124)	MP (N=193)	Thal/Dex (N=234)	Plac/Dex (N=232)
DVT/PE adverse events				
Patients with at least 1 DVT/PE	16 (12.9)	14 (7.3)	44 (18.8)	13 (5.6)
Patients with at least 1 DVT/PE that led to discontinuation of study drug	6 (4.8)	0 (0.0)	13 (5.6)	4 (1.7)
Patients with at least 1 DVT/PE that led to interruption or reduction of study drug	3 (2.4)	0 (0.0)	19 (8.1)	3 (1.3)
Patients that died due to a DVT/PE	0 (0.0)	2 (1.0)	3 (1.3)	1 (0.4)
Neuropathy adverse events				
Patients with at least 1 neuropathy AE	69 (55.6)	8 (4.1)	88 (37.6)	48 (20.7)
Patients with at least 1 neuropathy AE that led to discontinuation of study drug	22 (17.7)	0 (0.0)	17 (7.3)	2 (0.9)
Patients with at least 1 neuropathy AE that led to interruption or reduction of study drug	30 (24.2)	0 (0.0)	19 (8.1)	2 (0.9)
Patients that died due to a neuropathy AE	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Cardiac adverse events				
Patients with at least 1 cardiac AE	15 (12.1)	11 (5.7)	89 (38.0)	60 (25.9)
Patients with at least 1 cardiac AE that led to discontinuation of study drug	2 (1.6)	0 (0.0)	7 (3.0)	5 (2.2)
Patients with at least 1 cardiac AE that led to interruption or reduction of study drug	4 (3.2)	0 (0.0)	21 (9.0)	11 (4.7)
Patients that died due to a cardiac AE	1 (0.8)	4 (2.1)	4 (1.7)	7 (3.0)
Rash/Skin Reaction adverse events				
Patients with at least 1 rash/skin reaction AE	13 (10.5)	7 (3.6)	63 (26.9)	52 (22.4)
Patients with at least 1 rash/skin reaction AE that led to discontinuation of study drug	6 (4.8)	1 (0.5)	4 (1.7)	0 (0.0)
Patients with at least 1 rash/skin reaction AE that led to interruption or reduction of study drug	2 (1.6)	0 (0.0)	6 (2.6)	3 (1.3)
Patients that died due to a rash/skin reaction AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

- Serious adverse event/deaths/other significant events

In Study IFM 99-06, serious adverse events were reported for 38.7% (48/124) of patients in the MPT group and 29.5% (57/193) of patients in the MP group. Those reported by > 2% of patients in either of the treatment groups are summarized in Table 27. In the MPT group, pulmonary embolism and deep vein thrombosis, pneumonia pyrexia and back pain were the most frequently reported serious adverse events.

Table 27: Most frequently-observed (> 2%) serious adverse events (study IFM 99-06)

	Number (%) of patients	
Preferred Term[a]	MP Group (N=193)	MPT Group (N=124)
Pulmonary embolism	4 (2.1)	4 (3.2)
Deep vein thrombosis	1 (0.5)	4 (3.2) *
Pneumonia	2 (1.0)	3 (2.4) *
Pyrexia	2 (1.0)	3 (2.4) *
Back pain	1 (0.5)	3 (2.4) *
General physical health deterioration	5 (2.6)	2 (1.6)
Lung disorder	6 (3.1) **	1 (0.8)
Disease progression	5 (2.6) **	1 (0.8)
Septic shock	4 (2.1) **	1 (0.8)
Anaemia	6 (3.1) **	0

* Incidence at least 2-fold greater than in the MP group (where the incidence in the MPT group was ≥ 1%).

** Incidence at least 2-fold greater than in the MPT group (where the incidence in the MP group was ≥ 1.6%).

Table 28: Most frequently-observed (> 2%) serious adverse events (study THAL-MM-003)

Preferred Term[a]	Number (%) of patients Thalidomide / Dexamethasone (N=234)	Number (%) of patients Placebo / Dexamethasone (N=232)
Patients with at least 1 serious adverse event	148 (63.2)	119 (51.3)
Deep vein thrombosis	22 (9.4)*	4 (1.7)
Pneumonia NOS	21 (9.0)	19 (8.2)
Pulmonary embolism	16 (6.8)*	5 (2.2)
Atrial fibrillation	8 (3.4)	6 (2.6)
Bronchopneumonia NOS	6 (2.6)	5 (2.2)
Cerebrovascular accident	6 (2.6)	2 (0.9)
Hyperglycaemia NOS	6 (2.6)	6 (2.6)
Syncope	5 (2.1)	0 (0.0)
Anaemia NOS	5 (2.1)	1 (0.4)
Renal failure NOS	4 (1.7)	8 (3.4)
Pyrexia	3 (1.3)	5 (2.2)

Throughout the study period, a total of 35 deaths were recorded (18 in the MP group, 7 in the MPT group, and 10 in the MEL100 group). General and physical deterioration [3 (2.4%)] was most frequently reported in the MPT group. There were a total of 125 deaths in a study THAL-MM-003 (57 in the thalidomide/dexamethasone treatment group and 68 in the placebo/dexamethasone treatment group). In the thalidomide/dexamethasone group, 42% (24/57) of deaths were due to disease progression *versus* 59% (40/68) in the placebo/dexamethasone group.

- Laboratory findings

Myelosuppression was increased when thalidomide was added to MP or dexamethasone, especially the incidence of neutropenia and leucopenia was higher in the MPT treatment group compared with the MP treatment group (see table 29, 30 and 31).

Table 29: Shifts in haematology parameters from normal baseline to worst grade (WHO toxicology code) during treatment (study IFM 99-06)

Parameter	N[a]	Number (%) of Patients Grade 1	Grade 2	Grade 3	Grade 4	Total
Melphalan / Prednisone (N=193)						
Hemoglobin (g/dL)	173	22 (28.6)	7 (9.1)	4 (5.2)	0 (0.0)	77 (100.0)
Neutrophils (10^9/L)	173	28 (20.4)	33 (24.1)	16 (11.7)	0 (0.0)	137 (100.0)
Platelets (10^3/mm^3)	157	22 (13.2)	15 (9.0)	10 (6.0)	2 (1.2)	167 (100.0)
WBC (10^9/L)	173	51 (42.1)	39 (32.2)	11 (9.1)	0 (0.0)	121 (100.0)
Melphalan / Prednisone / Thalidomide / (N=124)						
Hemoglobin (g/L)	115	13 (27.7)	8 (17.0)	1 (2.1)	0 (0.0)	47 (100.0)
Neutrophils (10^9/L)	102	17 (19.1)	31 (34.8)	13 (14.6)	5 (5.6)	89 (100.0)
Platelets (10^3/mm^3)	114	9 (8.0)	9 (8.0)	4 (3.5)	7 (6.2)	113 (100.0)
WBC (10^9/L)	115	23 (31.9)	32 (44.4)	10 (13.9)	0 (0.0)	72 (100.0)

[a] Nbr of patients with baseline and post-baseline measurements. WBC=white blood cells; WHO=World Health Organization

Table 30: Comparison of haematological disorders for the melphalan, prednisone (MP) and melphalan, prednisone, thalidomide (MPT) combinations in study IFM 99-06

	n (% of patients) MP (n=193)	n (% of patients) MPT (n=124)
	Grades 3 and 4*	
Neutropenia	57 (29.5)	53 (42.7)
Leukopenia	32 (16.6)	32 (25.8)
Anaemia	28 (14.5)	17 (13.7)
Lymphopenia	14 (7.3)	15 (12.1)
Thrombocytopenia	19 (9.8)	14 (11.3)

* WHO Criteria

Table 31: Shifts in haematology parameters from normal baseline to worst NCI CTC grade during treatment (study THAL-MM-003)

		Number (%) of Patients			
Parameter	**N at Baseline**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Thalidomide / Dexamethasone (N=234)					
ANC (GI/L)	219	37 (16.9)	18 (8.2)	3 (1.4)	1 (0.5)
Hemoglobin (g/L)	220	38 (17.3)	5 (2.3)	0 (0.0)	0 (0.0)
Lymphocytes (GI/L)	219	0 (0.0)	58 (26.5)	17 (7.8)	0 (0.0)
Platelets (GI/L)	215	7 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)
WBC (GI/L)	220	37 (16.8)	13 (5.9)	2 (0.9)	0 (0.0)
Placebo / Dexamethasone (N=232)					
ANC (GI/L)	210	21 (10.0)	10 (4.8)	5 (2.4)	1 (0.5)
Hemoglobin (g/L)	215	23 (10.7)	3 (1.4)	0 (0.0)	1 (0.5)
Lymphocytes (GI/L)	213	0 (0.0)	51 (23.9)	14 (6.6)	0 (0.0)
Platelets (GI/L)	213	22 (10.3)	1 (0.5)	0 (0.0)	1 (0.5)
WBC (GI/L)	215	26 (12.1)	12 (5.6)	2 (0.9)	1 (0.5)

ANC=absolute neutrophil count; NCI CTC=National Cancer Institute Common Toxicity Criteria; WBC=white blood cells

- Safety in special populations

No safety analysis in special populations was performed in study IFM 99-06. Data from studies Thal-MM-003 or E1A00 did not show any gender difference regarding adverse effects (data not shown).

- Safety related to drug-drug interactions and other interactions

There we no safety analysis of drug-drug interactions studies (see also clinical pharmacokinetic interaction studies).

- Discontinuation due to adverse events

The rates of discontinuation due to AEs across the 3 controlled studies (IFM-99-006, THAL-MM-003, and E1A00) were higher in thalidomide treated patients than in the control arms (see tables 32 and 33). In the IFM-99-06 study, more patients experienced AEs leading to discontinuation of study drug in the MPT group (42.7%; 53/124) compared to the MP group (7.8%; 15/193). Peripheral neuropathy (8.9%), neutropenia (5.6%) and paresthesia (4.0%) were the most frequently observed AEs resulting in discontinuation of study drug in the MPT group.

Table 32: Reasons for discontinuation of treatment (study IFM 99-06, ITT population)

	Number of Subjects		
Reason[a]	**MP (N=196)**	**MPT (N=125)**	**MEL100 (N=126)**
First Progression of Disease	128	29	68
Subject Decision to Discontinue	2	1	2
Treatment toxicity[b]	5	15 [d]	8
Thalidomide toxicity[c]	NA	45	NA
Death	18	7	10
Other	12	1	14

[a] Several reasons for discontinuation could be given.
[b] Toxicity not associated with thalidomide in the opinion of the local investigator. Note that the toxicity may not have been reported as an adverse event.
[c] Toxicity considered by the local investigator to be due to thalidomide. Note that the toxicity may not have been reported as an adverse event.
[d] Includes one subject (Subject 040) for whom toxicity was reported as being related both to study treatment and to thalidomide.

Table 33: Reasons for discontinuation of treatment (study THAL-MM-003, ITT Population)

Reason	Number (%) of Patients	
	Thalidomide/Dexamethasone (N=235)	Placebo/Dexamethasone (N=235)
Adverse Event[a]	57 (24.3)	19 (8.1)
Progression of Disease[b]	1 (0.4)	1 (0.4)
Lack of Therapeutic Effect	68 (28.9)	145 (61.7)
Patient Declined Further Study Participation	15 (6.4)	16 (6.8)
Patient Lost to Follow-Up	0 (0.0)	1 (0.4)
Death	23 (9.8)	24 (10.2)
Major Protocol Violation[c]	0 (0.0)	4 (1.7)
Other[d]	9 (3.8)	6 (2.6)

[a] Taken from the discontinuation page of the patient's case report form. A patient may have experienced an adverse event leading to discontinuation of 1 or both study drugs, but still remain in the study, or discontinue the study for reasons other than adverse event.
[b] Taken from the "other" field when indication was progressive disease.
[c] Taken from the discontinuation page of the patient's case report form.
[d] Included deviations from inclusion/exclusion criteria, non-compliance with study drug, concomitant medication non-compliance, missing or out-of-window visits or assessments, and other.

- Post marketing experience

Safety information from PSURs for Thalidomide Pharmion marketing authorization in Australia in (October 2003) and compassionate use in France was provided. Calculation of patient exposure was based upon data obtained through the Pharmion Risk Management Plan (PRMP) that requires patients, physicians, and pharmacists to be registered in order to receive the product. The number of patients treated with Thalidomide Pharmion 50 mg was estimated to 21 347 patients, corresponding to approximately 2 175 409 patient-days of exposure. The majority (> 90%) of patients were adults (age > 18 years) and most received thalidomide for multiple myeloma (75%) or other life-threatening diseases. Thalidomide Laphal 50 mg or 100 mg capsule exposure is estimated at 9 213 patients. The mean age of patients was ≥ 52.4 years. Very few patients were < 18 years old. More than half of the patients had an indication of multiple myeloma.

Published reports of adverse events in multiple myeloma involved more than 4 500 patients. The most common adverse events associated with thalidomide use in patients with multiple myeloma reported in the literature were similar to those reported in studies IFM-99-06, THAL-MM-003, and E1A00 and included constipation, sedation/somnolence, peripheral neuropathy, fatigue/weakness, rash, and dizziness. Serious adverse events included peripheral neuropathy, deep vein thrombosis and pulmonary embolism, bradycardia, and severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis.

Publications of adverse events in other indications involve more than 3 300 patients dating back to the early 1980s. The adverse events reported in these studies are consistent with the known toxicity profile of thalidomide. Additional adverse reactions related to post-marketing experience with thalidomide and not seen in the pivotal study include: toxic epidermal necrolysis, intestinal obstruction, hypothyroidism and sexual dysfunction.

- Discussion on clinical safety

Teratogenicity

Thalidomide is a potent human teratogen, inducing a high frequency (about 30%) of severe and life-threatening birth defects such as: ectromelia (amelia, phocomelia, hemimelia) of the upper and/or lower extremities, microtia with abnormality of the external acoustic meatus (blind or absent), middle and internal ear lesions (less frequent), ocular lesions (anophthalmia, microphthalmia), congenital heart disease, renal abnormalities. Other less frequent abnormalities have also been described. Therefore, thalidomide is contraindicated during pregnancy and in women of childbearing potential unless all the conditions of the pregnancy prevention programme are met (see SPC section 4.3).

Women of childbearing potential must use one effective method of contraception for 4 weeks before therapy, during therapy, and during 4 weeks after thalidomide therapy (see SPC section 4.4). If

pregnancy occurs in a woman treated with thalidomide, treatment must be stopped immediately and the patient should be referred to a physician specialised or experienced in teratology for evaluation and advice. As thalidomide is found in semen, male patients must use condoms during treatment and for 1 week after dose interruption and/or cessation of treatment when having sexual intercourse with a pregnant woman or with a woman with childbearing potential who is not using effective contraception. If pregnancy occurs in a partner of male patient taking thalidomide, the female partner should be referred to a physician specialised or experienced in teratology for evaluation and advice. It is unknown whether thalidomide is excreted in human breast milk. Animal studies have shown excretion of thalidomide in breast milk. Therefore breast-feeding should be discontinued during therapy with thalidomide (see SPC section 4.6).

For women of childbearing potential, prescriptions should be limited to 4 weeks of treatment and continuation of treatment requires a new prescription. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day. Dispensing of thalidomide should occur within a maximum of 7 days of the prescription. For all other patients, prescriptions should be limited to 12 weeks and continuation of treatment requires a new prescription. Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of treatment.

A female patient or a female partner of a male patient is considered to have childbearing potential unless she meets at least one of the following criteria: Age ≥ 50 years and naturally amenorrhoeic for ≥ 1 year (Amenorrhoea following cancer therapy does not rule out childbearing potential); Premature ovarian failure confirmed by a specialist gynaecologist; Previous bilateral salpingo-oophorectomy, or hysterectomy; XY genotype, Turner's syndrome, uterine agenesis.

Patients should not donate blood or semen during therapy or for 1 week following discontinuation of thalidomide.

Counselling
For women of childbearing potential, thalidomide is contraindicated unless all of the following are met:

- She understands the teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 4 weeks before starting treatment, throughout the entire duration of treatment, and 4 weeks after the end of treatment
- Even if a woman of childbearing potential has amenorrhea she must follow all the advice on effective contraception
- She should be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy
- She understands the need to commence the treatment as soon as thalidomide is dispensed following a negative pregnancy test
- She understands the need and accepts to undergo pregnancy testing every 4 weeks
- She acknowledges that she understands the hazards and necessary precautions associated with the use of thalidomide.

As thalidomide is found in semen, male patients taking thalidomide must meet the following conditions:

- Understand the teratogenic risk if engaged in sexual activity with a pregnant woman.
- Understand the need for the use of a condom if engaged in sexual activity with a pregnant woman or a woman of childbearing potential not using effective contraception.

The prescriber must ensure that:

- The patient complies with the conditions of the pregnancy prevention programme
- The patient confirms that he (she) understand the aforementioned conditions.

Contraception
Women of childbearing potential must use one effective method of contraception for 4 weeks before therapy, during therapy, and during 4 weeks after thalidomide therapy and even in case of dose

interruption unless the patient commits to absolute and continuous abstinence confirmed on a monthly basis. If not established on effective contraception, the patient must be referred preferably to an appropriately trained health care professional for contraceptive advice in order that contraception can be initiated.
The following can be considered to be examples of effective methods of contraception: Subcutaneous hormonal implant, levonorgestrel-releasing intrauterine system (IUS), medroxyprogesterone acetate depot, tubal sterilisation, sexual intercourse with a vasectomised male partner only; vasectomy must be confirmed by two negative semen analyses, ovulation inhibitory progesterone-only pills (i.e., desogestrel).

Because of the increased risk of venous thromboembolism in patients with multiple myeloma, combined oral contraceptive pills are not recommended (see SPC section 4.5). If a patient is currently using combined oral contraception the patient should switch to one of the effective method listed above. The risk of venous thromboembolism continues for 4−6 weeks after discontinuing combined oral contraception.

Pregnancy testing
Medically supervised pregnancy tests with a minimum sensitivity of 25 IU/ml must be performed for women of childbearing potential. This requirement includes women of childbearing potential who practice absolute and continuous abstinence. A medically supervised pregnancy test should be performed during the consultation, when thalidomide is prescribed or in the 3 days prior to the visit to the prescriber once the patient had been using effective contraception for at least 4 weeks. The test should ensure the patient is not pregnant when she starts treatment with thalidomide. A medically supervised pregnancy test should be repeated every 4 weeks, including 4 weeks after the end of treatment. These pregnancy tests should be performed on the day of the prescribing visit or in the 3 days prior to the visit to the prescriber.

Educational materials
In order to assist patients in avoiding foetal exposure to thalidomide and to provide additional important safety information, the Marketing Authorisation holder will provide educational material to healthcare professionals. The pregnancy prevention programme of the risk management plan reinforces the warnings about the teratogenicity of thalidomide, provides advice on contraception before therapy is started and provides guidance on the need for pregnancy testing. Full patient information about the teratogenic risk and the pregnancy prevention measures as specified in the pregnancy prevention programme of the risk management plan should be given by the physician to women of childbearing potential and, as appropriate, to male patients.

The risk management plan was considered adequate to address the issue of teratogenicity and other safety concerns.

Other thalidomide treatment related risks

A total of patients received thalidomide in the clinical trials of this application (124 in study IFM 99-06 in combination with melphalan and prednisone; 234 in study THAL-MM-003 and 102 in study E1A00 in combination with dexamethasone). The median exposure to thalidomide ranged between 10 and 30 weeks. Post-approval safety information on thalidomide has been reported in PSURs and was based on an estimated exposure of about 21 000 patients.

The most commonly observed adverse reactions associated with the use of thalidomide in combination with melphalan and prednisone are: neutropenia, leukopenia, constipation, somnolence, paraesthesia, peripheral neuropathy, anaemia, lymphopenia, thrombocytopenia, dizziness, dysaesthesia, tremor and peripheral oedema. The clinically important adverse reactions associated with the use of thalidomide in combination with melphalan and prednisone or dexamethasone include: deep vein thrombosis (DVT) and pulmonary embolism (PE), peripheral neuropathy, severe skin reactions including Stevens Johnson syndrome and toxic epidermal necrolysis, syncope, bradycardia, and dizziness (see SPC sections 4.2, 4.4, 4.5 and 4.8).

An increased risk of DVT and PE has been reported in patients treated with thalidomide (study IFM 99-06: 12.9% in the MPT group vs. 7.3% in the MP group; study THAL-MM-003: 18.8% in thalidomide/dexamethasone group vs. 5.6% in placebo/dexamethasone group). This risk is also

reported in literature. The risk appears to be greatest during the first 5 months of therapy. Previous history of thromboembolic events or concomitant administration of erythropoietic agents or other agents such as hormone replacement therapy, may also increase thrombotic risk in these patients. Therefore, these agents should be used with caution in multiple myeloma patients receiving thalidomide with prednisone and melphalan. Particularly, a haemoglobin concentration above 12g/dl should lead to discontinuation of erythropoietic agents. If the patient experiences any thromboembolic events, treatment must be discontinued and standard anticoagulation therapy started. Once the patient has been stabilised on the anticoagulation treatment and any complications of the thromboembolic event have been managed, the thalidomide treatment may be restarted at the original dose dependent upon a benefit risk assessment. The patient should continue anticoagulation therapy during the course of thalidomide treatment (see SPC section 4.2). Thromboprophylaxis should be administered for at least the first 5 months of treatment especially in patients with additional thrombotic risk factors. Prophylactic antithrombotic medicinal products, such as low molecular weight heparins or warfarin, should be recommended. The decision to take antithrombotic prophylactic measures should be made after careful assessment of an individual patient's underlying risk factors (see SPC section 4.2). Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, arm or leg swelling (see SPC section 4.4).

Multiple dose administration of 200 mg thalidomide q.d. for 4 days had no effect on the international normalized ratio (INR) in healthy volunteers. However, due to the increased risk of thrombosis in cancer patients, and a potentially accelerated metabolism of warfarin with corticosteroids, close monitoring of INR values is advised during thalidomide-prednisone combination treatment as well as during the first weeks after ending these treatments (see SPC section 4.5). Thalidomide does not interact with hormonal contraceptives. In 10 healthy women, the pharmacokinetic profiles of norethindrone and ethinyl estradiol following administration of a single dose containing 1.0 mg of norethindrone acetate and 0.75 mg of ethinyl estradiol were studied. The results were similar with and without co-administration of thalidomide 200 mg/day to steady-state levels. However, combined hormonal contraceptives are not recommended due to the increased risk of venous thrombo-embolic disease (see SPC section 4.5).

Peripheral neuropathy is a very common, potentially severe, adverse reaction to treatment with thalidomide that may result in irreversible damage (see SPC sections 4.4 and 4.8). The percentage of patients with neuropathy events was 55.6% in the MPT groups vs. 4.1% in MP in study IFM 99-06, and 37.6% in the thalidomide/dexamethasone group vs. 20.7% in placebo/dexamethasone group in study THAL-MM-003. Peripheral neuropathy generally occurs following chronic use over a period of months. However, reports following relatively short-term use also exist. Incidence of neuropathy events leading to discontinuation, dose reduction or interruption increases with cumulative dose and duration of therapy. If the patient experiences peripheral neuropathy, dose and schedule modification should be performed as described in table 34.

Table 34: Recommended dose modifications for Thalidomide Pharmion related neuropathy in first line treatment of multiple myeloma.

Severity of neuropathy	**Modification of dose and regimen**
Grade 1 (paraesthesia, weakness and/or loss of reflexes) with no loss of function	Continue to monitor the patient with clinical examination. Consider reducing dose by up to 50% if symptoms worsen.
Grade 2 (interfering with function but not with activities of daily living)	Reduce dose by up to 50% or interrupt treatment and continue to monitor the patient with clinical and neurological examination. If no improvement or continued worsening of the neuropathy, discontinue treatment. If the neuropathy resolves to Grade 1 or better, the treatment may be restarted at 50% of the last dose, if the benefit/risk is favourable.
Grade 3 (interfering with activities of daily living)	Discontinue treatment
Grade 4 (neuropathy which is disabling)	Discontinue treatment

Paresthesia was reported in study IFM 99-06, with an incidence of 18.5% of patients in the MPT group compared with 2.1% in the MP group. Peripheral neuropathy (MPT: 16.9% vs. MP: 0), dysaesthesia (MPT: 12.1% vs. MP: 0.5%), and neuropathy (MPT: 12.1% vs. MP: 0) were all events that were also reported in >10% of patients in the thalidomide treatment group. Careful monitoring of patients for symptoms including paraesthesia, dysaesthesia, discomfort, abnormal co-ordination or weakness is recommended (see SPC section 4.4). It is recommended that clinical and neurological examinations are performed in patients prior to starting thalidomide therapy, and that routine monitoring is carried out regularly during treatment. Medicinal products known to be associated with neuropathy (e.g. vincristine and bortezomib) should be used with caution in patients receiving thalidomide (see SPC section 4.5). Thalidomide may also potentially aggravate existing neuropathy and should therefore not be used in patients with clinical signs or symptoms of peripheral neuropathy unless the clinical benefits outweigh the risks.

Cardiac events were higher in patients taking thalidomide (study IFM 99-06 MPT: 12.1% vs. MP: 5.7%; study THAL-MM-003: 38.0% in thalidomide/dexamethasone group vs. 25.9%). In these patients, the most frequent cardiac events were hypotension, bradyarrhythmia, bradycardia, sinus bradycardia, myocardial ischemia, and atrial fibrillation. In literature, sinus bradycardia, sometimes associated with syncopal episodes has been reported in multiple myeloma patients. Due to the potential for thalidomide to induce bradycardia, caution should be exercised with medicinal products having the same pharmacodynamic effect such as drugs known to induce torsade de pointes, beta blockers or anticholinesterase agents (see SPC section 4.5).

Treatment recommendations for thalidomide-associated haematologic toxicities are limited. When thalidomide is used in combination with chemotherapy, granulocyte colony stimulating factor (G-CSF) has been used to allow continued administration of the chemotherapy on schedule and to limit the number of neutropenic days. Adverse reactions for thalidomide related haematological disorders compared to the comparator arm are provided in section 4.8 of the SPC, as the comparator has a significant effect on these disorders.

In the clinical trials, skin eruption and rash were commonly reported. Moribilliform, seborrhoea, maculopapular, or non-specific dermatitis were also described in the literature. Severe adverse events such as exfoliative erythroderma, erythema multiforme and toxic epidermal necrolysis (TEN), were reported and generally occurred when thalidomide was given in combination with dexamethasone. If at anytime the patient experiences a toxic skin reaction e.g. Stevens-Johnson syndrome, the treatment should be discontinued permanently.

Thalidomide has sedative properties thus may enhance the sedation induced by anxiolytics, hypnotics, antipsychotics, H1 anti-histamines, opiate derivatives, barbiturates and alcohol. Caution should be used when thalidomide is given in combination with medicinal products that cause drowsiness (see SPC section 4.5). The medicinal product should be taken as a single dose at bedtime, to reduce the impact of somnolence. In addition, patients should be instructed to avoid situations where somnolence may be a problem and to seek medical advice before taking other medicinal products known to cause somnolence. They should be advised as to the possible impairment of mental and/or physical abilities required for the performance of hazardous tasks (see SPC section 4.7). Patients should be monitored and dose reduction may be required.

No specific dose adjustments are recommended for the elderly. Thalidomide has not formally been studied in patients with impaired renal or hepatic function. No specific dose recommendations for these patient populations are available. Patients with severe organ impairment should be carefully monitored for adverse effects. Thalidomide is not recommended for use in children below 18 years of age as safety and efficacy have not been established.
Patients with hypersensitivity to thalidomide or to any of the excipients of Thalidomide Pharmion should not take this medicinal product. In addition, the capsules of Thalidomide Pharmion contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

1.5. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan
The MAA submitted a risk management plan, which included a risk minimisation plan.

Table 35: Summary of the risk management plan

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimization Activities (routine and additional)
Identified risks		
Teratogenicity	• Routine pharmacovigilance – Expedited reporting of all pregnancies as a serious event. – Optimize data collection and reporting of pregnancies by Pregnancy adverse event forms – Follow-up of all pregnancies until outcome and until the final diagnosis in cases of congenital malformation – Review of 6-monthly PSURs (periodic and cumulative) – Examination of demographic data in PSURs. • Ongoing cumulative updates • 6-monthly line-listings to be submitted to the authorities • Thalidomide Pharmion PPP procedures to be applied to all Pharmion sponsored studies and all compassionate use.	• Section 4.3 of the SPC - Contraindicated in pregnant women and in women of childbearing potential unless all the conditions of the Thalidomide Pharmion PPP are met. • Section 4.4 of the SPC - Warnings o Criteria for women of non-childbearing potential o Counselling o Contraception o Pregnancy testing o Precautions for men o Prescribing and dispensing restrictions o Additional precautions o Reference to educational materials. • Section 4.6 of the SPC – Warnings, contraception information and pregnancy advice provided. Information on lactation also provided. • Listed ADR in Section 4.8 of the SPC • Pregnancy Prevention Programme o Educational Programme - Direct HCP communication prior to launch - Educational material for healthcare professionals and patients ▪ HCP booklets, patient assessment algorithm, patient treatment initiation forms, patient card or equivalent tools. ▪ Patient booklets o Therapy management: - Criteria for determining women of childbearing potential (WCBP), effective contraceptive measures for WCBP, regular pregnancy testing for WCBP - Advise provided by SPC, outlined in direct HCP communication and detailed in Educational materials.

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimization Activities (routine and additional)
Identified risks		
Peripheral neuropathy	• Routine pharmacovigilance • 6-monthly line-listings to be submitted to the authorities • Further evaluation of a possible dose dependency to be provided by the OPTIMUM study.	• Section 4.2 of the SPC - Details on dose reduction, interruption and discontinuation in the event of development of neuropathy. • Section 4.4 of the SPC - Warnings about peripheral neuropathy and recommendations for routine monitoring. • Section 4.5 of the SPC - Warning regarding the use of other medicinal products known to cause neuropathy. • Listed as ADR in Section 4.8 of SPC - Details the frequency of peripheral neuropathy events. • Direct HCP communication prior to launch. • Educational material for healthcare professionals and patients
Thromboembolic events	• Routine pharmacovigilance • 6-monthly line-listings to be submitted to the authorities • Further evaluation of the risk of thromboembolic events and any possible dose dependency will be provided by the OPTIMUM study • Further characterization of recommendations on antithrombotic prophylactic measures to be provided to prescribers for preventing thromboembolic events in thalidomide patients (GIMEMA-MM-03-05 and Myeloma IX studies).	• Section 4.2 of the SPC - Recommendations for the use of anticoagulation prophylaxis and details on the discontinuation of thalidomide treatment and start of anticoagulation therapy with advice on subsequent restarting of treatment. • Section 4.4 of the SPC – Warnings regarding thrombotic risk factors. • Listed as ADR in Section 4.8 of the SPC -Details the frequency of thromboembolic events. • Direct HCP communication prior to launch. • Educational material for healthcare professionals and patients
Severe skin reactions	• Routine pharmacovigilance.	• Section 4.2 of the SPC - Highlights the need to monitor skin disorders. • Section 4.3 of the SPC - Contraindication in patients with known hypersensitivity to thalidomide or to any of the excipients • Section 4.4 of the SPC - Warnings and details of treatment discontinuation if a patient experiences a toxic skin reaction (eg, Stevens-Johnson). • Listed as ADR in Section 4.8 of the SPC - Details the frequency of skin and subcutaneous tissue disorders. • Direct HCP communication prior to launch. • Educational material for healthcare professionals and patients

Bradycardia/syncope	• Routine pharmacovigilance • 6-monthly line-listings to be submitted to the authorities • Further evaluation of a possible dose dependency to be provided by the OPTIMUM.	• Section 4.4 of the SPC - Warnings regarding the need to monitor for bradycardia/syncope. • Section 4.5 of the SPC - Warning against use of other medicinal products known to cause bradycardic effects. • Listed as ADR in Section 4.8 of the SPC - Details the frequency of bradycardia and syncope. • Direct HCP communication prior to launch. • Educational material for healthcare professionals and patients
Somnolence	• Routine pharmacovigilance.	• Section 4.2 of the SPC - Recommendations on administration to reduce the impact of somnolence. • Section 4.4 of the SPC - Warnings regarding somnolence and how to manage this risk. • Section 4.5 of the SPC - Warning regarding the interaction with other medicinal products that cause drowsiness. • Listed as ADR in Section 4.8 - Details the frequency of somnolence. • Direct HCP communication prior to launch. • Educational material for healthcare professionals and patients
Dizziness	• Routine pharmacovigilance.	• Listed as ADR in Section 4.8 - Details the frequency of dizziness.
Neutropenia/ leukopenia	• Routine pharmacovigilance.	• Listed as ADR in Section 4.8 of the SPC - Hematological adverse reactions for both thalidomide and the comparator treatment are outlined in this document, since the comparator has a significant effect on these disorders
Gastrointestinal disorders	• Routine pharmacovigilance.	• Listed as ADR in Section 4.8 of the SPC - Details the frequency of gastrointestinal disorders.
Thyroid dysfunction and hypothyroidism	• Routine pharmacovigilance.	• Listed as ADR in Section 4.8 of the SPC

Potential risks		
Interaction with oral contraceptives	• Routine pharmacovigilance.	• Sections 4.4 of the SPC - Warnings about increased risk of venous thromboembolism with combined oral contraceptive pills • Section 4.5 of the SPC - Interaction
Off-label use	• Routine pharmacovigilance. • Drug utilization studies (collection of demographics and indication).	• Direct HCP communication prior to launch. • Educational material for healthcare professionals and patients
Missing information		
• Specific studies in hepatic impairment	• Routine pharmacovigilance.	• Section 4.2 of the SPC- Recommendations for patients with severe hepatic impairment • Section 4.4 of the SPC - Warnings for monitoring for adverse reactions in patients with severe hepatic impairment
• Specific studies in MM patients with renal impairment	• Routine pharmacovigilance.	• Section 4.2 of the SPC- Recommendations for patients with severe renal impairment • Section 4.4 of the SPC- Warnings for monitoring for adverse reactions in patients with severe renal impairment
• Pediatric patients	• Routine pharmacovigilance.	• Section 4.2 of the SPC- Provides recommendations to not use Thalidomide Pharmion in children below 18 years of age.
• Women who are breastfeeding	• Routine pharmacovigilance.	• Section 4.6 of the SPC- Provides appropriate information for discontinuation of breast-feeding during therapy with thalidomide.

The CHMP, having considered the data submitted in the application is of the opinion that the following risk minimisation activities as detailed above are necessary for the safe and effective use of the medicinal product (see benefit-risk assessment).

1.6. Overall conclusions, risk/benefit assessment and recommendation

Quality

The drug substance and the drug product have been appropriately described and generally satisfactory documentation has been provided. The excipients used in the preparation of the drug product and manufacturing process selected are standard for capsules preparation. The results indicate that the drug substance and the drug product can be reproducibly manufactured.

Non-clinical pharmacology and toxicology

The pharmacological mechanisms of thalidomide and the spectrum of its activity is not fully characterised. Thalidomide shows immunomodulatory anti-inflammatory and potential anti-neoplastic activities. Data from *in vitro* studies and clinical trials suggest that the immunomodulatory, anti-inflammatory and anti-neoplastic effects of thalidomide may be related to suppression of excessive tumour necrosis factor-alpha (TNF-α) production, down-modulation of selected cell surface adhesion molecules involved in leukocyte migration and anti-angiogenic activity. Although a variety of mechanisms of action have been elucidated, it remains unclear which one or more of these play a role in the treatment of multiple myeloma. Thalidomide is a proven teratogen in humans. Animal studies have demonstrated differences in species susceptibility to the teratogenic effects of thalidomide. No mutagenic or genotoxic effect has been revealed when thalidomide was assayed in a standard battery of genotoxicity tests. No evidence of carcinogenicity was observed at exposures approximately 15, 13 and 39 times the estimated clinical AUC at the recommended starting dose in mice, male rats and female rats respectively.

Efficacy

Results from IFM 99-06, a phase III, randomised, open label, parallel group, multicentre study have demonstrated a survival advantage when thalidomide is used in combination with melphalan and prednisone for 12 cycles of 6 weeks in the treatment of newly diagnosed multiple myeloma patients. In this study the age range of patients was 65-75 years, with 41% (183/447) of patients 70 years old or older. The median dose of thalidomide was 217 mg and >40% of patients received 9 cycles. Melphalan and prednisone were dosed at 0.25 mg/kg/day and 2 mg/kg/day respectively on days 1 to 4 of each 6 weeks cycle.

Further to the per protocol analysis where a 21.4 month survival advantage (OS) over MP was noted with the MPT combination (hazard ratio=0.56, p=0.001), an update was conducted for the IFM 99-06 study providing an additional 15 months follow-up data. The median OS was 51.6 ± 4.5 and 33.2 ± 3.2 months in the MPT and MP groups, respectively (97.5% CI 0.42 to 0.84). This 18.4 month difference was statistically significant with a hazard ratio of reduction of risk of death in the MPT arm of 0.59 (p-value <0.001) and was consistent with the assumption made in the statistical analysis plan.

The superiority of MPT over MP was confirmed by prolonging progression free survival (PFS) and higher rates of response (including partial response, very good partial response, and complete response). The primary endpoint OS was not affected by treatment after progression (mainly VAD or alkylating agent-based regimens).

Safety

In three phase III randomised controlled trials, 124 patients with multiple myeloma were exposed to the melphalan/prednisone and thalidomide combination, and 336 to the thalidomide/dexamethasone combination. The median exposure to thalidomide ranged between 10 and 44 weeks. Post-approval safety information on thalidomide was provided from periodic safety update reports and based on an estimated exposure of about 21 000 patients.

The most commonly observed adverse reactions associated with the use of thalidomide are peripheral neuropathy, somnolence, paraesthesia, dizziness, dysaesthesia, tremor, neutropenia, leukopenia, anaemia, lymphopenia, thrombocytopenia, peripheral oedema and constipation.

The clinically important adverse reactions associated with the use of thalidomide deep vein thrombosis and pulmonary embolism, peripheral neuropathy, severe skin reactions including Stevens Johnson Syndrome and toxic epidermal necrolysis, syncope, bradycardia, and dizziness.

Thalidomide is a potent human teratogen, inducing a high frequency (about 30%) of severe and life-threatening birth defects. Thalidomide must never be used by women who are pregnant or could become pregnant. Conditions for the safe use of thalidomide are stated in the pregnancy prevention programme of the risk management plan and must be fulfilled for all male and female patients. In addition to the information included in the product information, risk minimisation activities include prescribing and dispensing restrictions, educational materials, continuous education and direct communication to health care professional prior to launch.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics. Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

In accordance with Article 78 (1) and 78 (2) in Title IV of Regulation (EC) No 726/2004, the EMEA and the CHMP have consulted both victims of thalidomide groups and patients' organisations, during the procedure for the assessment of the MAA. This consultation consisted of the involvement of two experts appointed by the relevant victim's and patient's organisations acting as individual experts, and the involvement of patients and victims acting as representatives of their organisations, based on the agreement of the applicant to disclose relevant confidential data, namely the package leaflet, the labelling and the risk management plan. In addition, readability tests were conducted by the applicant (including worst case scenario, i.e. 3 languages, multiple language leaflet) and passed user testing. Following the feedback of the CHMP and the EMEA quality review group, the layout of the leaflet was revised by the applicant to ensure readability whilst conforming to guidelines and paper size constraints. The applicant will investigate the utility of the landscape format for the three language leaflet whilst ensuring readability is not affected. The applicant confirmed that there will be a maximum of three languages on any insert as more than three would affect the readability. Multiple language inserts will only be used where a multi language package is assigned. When a multiple language leaflet is used, the list of local representatives is presented in normal text and mentioned only once.

Risk-benefit assessment

In a phase III, randomised, open label, parallel group, multicentre study (IFM 99-06), the clinical efficacy of thalidomide, in combination with melphalan and prednisone (MPT), has been demonstrated in terms of overall survival in patients with untreated multiple myeloma, ≥ 65 years or ineligible for high-dose chemotherapy, as compared to melphalan and prednisone (MP) alone. The 18-month increase in median survival and a hazard ratio of reduction of risk of death of 0.59 ($p<0.001$) for MPT over MP is considered the most important clinical benefit for patients with multiple myeloma since the MP treatment was established.

Most patients taking thalidomide in combination with melphalan and prednisone can be expected to experience adverse reactions such as neutropenia, leukopenia, constipation, somnolence, paraesthesia, peripheral neuropathy, anaemia, lymphopenia, thrombocytopenia, dizziness, dysaesthesia, tremor and peripheral oedema. Management and dosage recommendations for patients experiencing important adverse reactions such as deep vein thrombosis and pulmonary embolism, peripheral neuropathy, severe skin reactions including Stevens Johnson syndrome and toxic epidermal necrolysis, syncope, bradycardia, and dizziness are provided in the summary of product characteristics.

Thalidomide is a potent human teratogen, inducing a high frequency of severe and live-threatening birth defects. A risk management plan was submitted. Thalidomide is contraindicated during pregnancy and in women of childbearing potential unless all the conditions of the risk management plan are met. The CHMP, having considered the data submitted, was of the opinion that pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns. The following additional risk minimisation activities were required:

- Dear Healthcare Professional Letter to be sent at the time of the launch with the following message:
    - core text as agreed by the CHMP
    - national specific requirements agreed with the National Competent Authority regarding:
        - Distribution of the product
        - procedures to ensure that all appropriate measures have been performed prior to thalidomide being dispensed

- Educational Healthcare Professional's materials, containing the following elements:

- Healthcare Professional Booklet, including information on history of thalidomide; Posology; Prescription restrictions; Teratogenicity and the need to avoid foetal exposure; Obligations of healthcare professionals who intend to prescribe or dispense thalidomide (including the need to provide comprehensive advice and counselling to patients; that patients should be capable of complying with the requirements for the safe use of thalidomide; the need to provide patients with the appropriate patient educational material; reporting of any pregnancy, neuropathy or other AE (if applicable to a Member State) using the forms provided in the "Educational Healthcare Professional's Kit"; Safety advice relevant to all patients (including a description and management of thromboembolic and cardiovascular events, peripheral neuropathy; disposal of unwanted medicine; not to donate blood during treatment and for one week after treatment ends); Algorithm for pregnancy prevention plan implementation; Pregnancy Prevention Programme information (definition of women of childbearing potential (WCBP) and actions the physician should take if unsure; information on what is effective contraception; safety advice for WCPB and for men), pregnancy reporting requirements.
- Pregnancy initial and outcome reporting forms,
- Neuropathy and adverse reaction reporting forms,
- Treatment Initiation Forms for female patient of childbearing potential, female patient of non-childbearing potential and for male patient

Patient cards and/or equivalent tools including:

- verification that appropriate counselling has taken place
- documentation of childbearing status potential
- check box (or similar) which physician ticks to confirm that patient is using effective contraception (if female with childbearing potential)
- verification of initial negative pregnancy test prior to start of treatment (if female with childbearing potential)
- pregnancy test dates and results

- Educational patient booklets for female patient of childbearing potential, female patient of non-childbearing potential and for male patient, should contain the information that thalidomide is teratogenic, that it may cause thromboembolism, cardiovascular events and neuropathy, that it must not be given to any other person, that the patient should not donate blood, that the patient should tell their doctor about any adverse events, that any unused capsules should be returned to the pharmacist at the end of the treatment, and would include a description of the patient card and its use in the individual Member State and national or other applicable specific arrangements for a prescription for thalidomide to be dispensed.

The booklet for female patient of childbearing potential should also include information on the need to avoid foetal exposure, confirmation of pregnancy prevention method used, that if she needs to change or stop using her method of contraception she should inform: the physician prescribing her contraception that she is on thalidomide and the physician prescribing thalidomide that she has stopped or changed her method of contraception, the need for pregnancy test dates and results i.e. before treatment, every 4 weeks during treatment and after treatment, the need to stop Thalidomide Pharmion immediately upon suspicion of pregnancy, the need to contact their doctor immediately upon suspicion of pregnancy.

The booklet for male patients should also include information on the need to avoid foetal exposure, that thalidomide is found in semen and the need to use condoms if sexual partner is pregnant or is a women with childbearing potential not on effective contraception, that if his partner becomes pregnant he should inform his treating doctor immediately and always use a condom, that he should not donate semen.

- Prescription and dispensing restrictions:
The Member States shall put into place measures to ensure that the maximum treatment duration for one prescription shall be 4 weeks for women with childbearing potential, 12 weeks for men and women without childbearing potential. Prescriptions can only be dispensed within 7 days of the date of the prescription

Similarity with authorised orphan medicinal products

The applicant has claimed that Thalidomide Pharmion, at the time of submission of the application, is not similar to any of the authorised orphan medicinal products (as defined in Art. 3 of Commission Regulation (EC) No 847/2000) for a condition relating to the proposed therapeutic indication.
The Applicant has provided a report discussing the issue of similarity in regard to the authorised orphan medicinal product Revlimid (lenalidomide). In this report, the Applicant concluded on non-similarity with particular reference to the therapeutic indication.

The CHMP concluded that, having considered the arguments presented by the applicant, the Rapporteurs assessment and the conclusions of the Quality Working Party, Thalidomide Pharmion was similar, in terms of molecular structure (as defined in Art. 3 of Commission Regulation (EC) No 847/ 2000) to the orphan medicinal product Revlimid authorised for a condition relating to the proposed therapeutic indication. However, Thalidomide Pharmion and Revlimid did not share the same therapeutic indication, according to article 8 of Regulation (EC) No. 141/2000.

Therefore, CHMP is of the opinion that thalidomide is not similar to any authorised orphan medicinal products within the meaning of Article 3 of Commission Regulation (EC) No. 847/200 (See Appendix 1).

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consenus that the risk-benefit balance of Thalidomide Pharmion in the treatment of

Thalidomide Pharmion in combination with melphalan and prednisone as first line treatment of patients with untreated multiple myeloma, aged ≥ 65 years or ineligible for high dose chemotherapy.

Thalidomide Pharmion is prescribed and dispensed according to the Thalidomide Pharmion Pregnancy Prevention Programme (see section 4.4).

was favourable and therefore recommended the granting of the marketing authorisation.

And

In addition, the CHMP, with reference to Article 8 of Regulation EC No 141/2000, considers Thalidomide Pharmion not to be similar (as defined in Article 3 of Commission Regulation EC No. 847/2000) to Revlimid for the same therapeutic indication.

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