European Medicines Agency

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ASSESSMENT REPORT
FOR
Torisel

International non-proprietary name/Common name:
temsirolimus

Procedure No. EMEA/H/C/000799/II/0001

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

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SCIENTIFIC DISCUSSION

Introduction

Torisel (temsirolimus) was first granted a marketing authorisation in the EU on 19 Nov 2007 for first-line treatment of patients with advanced Renal Cell Carcinoma (RCC) who have at least 3 of 6 prognostic risk factors.

This type II variation concerns an extension of the indication for Torisel to add the new therapeutic indication: *"treatment of adult patients with relapsed and/or refractory mantle cell lymphoma (MCL)"*.

Torisel (temsirolimus) is a selective inhibitor of mTOR (mammalian target of rapamycin), a serine/threonine kinase involved in controlling many cellular functions, such as cell proliferation, cell survival, protein synthesis and transcription. Temsirolimus binds to an intracellular protein (FKBP-12), and the protein-temsirolimus complex inhibits the activity of mTOR that controls cell division. In treated tumour cells, inhibition of mTOR activity results in a G1 growth arrest caused by the disruption of translation of regulatory cell cycle proteins (D-type cyclins, c-myc, and ornithine decarboxylase). When mTOR is bound to the temsirolimus-FKBP-12 complex, its ability to phosphorylate and control the activity of protein translation factors that regulate cell division (4E-BP1 and S6K), is blocked. These protein translation factors are both downstream of mTOR in the P13 kinase/AKT pathway.

In addition to regulating cell cycle proteins, mTOR can regulate translation of the hypoxia-inducible factors, HIF-1 and HIF-2 alpha. These transcription factors regulate the ability of tumours to adapt to hypoxic microenvironments and to produce the angiogenic factor VEGF. Even though cyclin D1 mRNA is constitutively expressed in mantle cell lymphoma (MCL), it is potentially subject to translational regulation by a pathway involving the mammalian target of rapamycin (mTOR). In mantle cell lymphoma, mTOR kinase regulates mRNA translation by phosphorylation of two critical substrates—eukaryotic initiation factor 4E binding protein and p70S6 kinase. These phosphorylation events enhance translation of cyclin-D1 mRNA into cyclin-D1 protein.

Scope of the variation

This type II variation concerns an extension of indication to add treatment of adult patients with relapsed and/or refractory mantle cell lymphoma (MCL). Based on the results of the clinical development program for MCL, the recommended dosing regimen is different from that in advanced renal cell carcinoma. In this context, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.8, 4.9, 5.1, 5.2 and 6.6 of the SPC have been amended and the Package Leaflet has been updated accordingly. In addition, the MAH has taken the opportunity to make some minor editorial changes to the annexes and to update the contact details of the UK local representative in the Package Leaflet. The MAH has also updated annex IIB to include the version number of the latest Risk Management Plan (version 2.4) agreed with the CHMP.

This application is based on the final clinical study report for a phase 3 study in patients with relapsed and/or refractory MCL (study 3066K1-305-WW). In addition the following reports were included as part of the application:

- Population PK Analysis (CSR-70829): This is a summary of studies 3066K1-305-WW, 3066K1-124-US, -145-US, -200-US, and -203-EU;
- Study 3066K1-147-US (final clinical study report): a biomarker study in head and neck cancer that was ongoing at the time of the MAA for RCC;
- Study 3066K1-402-WW (final clinical study report): A completed phase 1/2 study of temsirolimus in combination with sunitinib;
- Study 3066K1-139-US (updated progress report): An ongoing study in paediatric patients, previously reported in the RCC MAA.

Mantle cell lymphoma

Non-Hodgkin Lymphomas can be seen as two major prognostic groups: the indolent lymphomas and the aggressive lymphomas. Mantle cell lymphoma (MCL) is a specific entity of B-cell lymphoma defined by the REAL classification (1994) and by the WHO classification (2001). The entity corresponds to the centrocytic lymphomas as defined previously by the Kiel classification (1988). Although MCL belongs to the group of indolent lymphomas the clinical course is rather more aggressive than in other entities of indolent lymphomas.

MCL accounts for approximately 8% of all lymphoma diagnoses. Patients with MCL are typically older adults with a male predominance and usually present with stage IV disease. The cells are characterized as $CD20^{+}$ $CD5^{+}$ $CD23^{-}$ with a t(11;14)(q13;q32) and cyclin D1 overexpression on immunohistochemistry. Response to chemotherapy usually results in a tumour response but unmaintained remissions are short and the median survival is 3 to 4 years. The treatment approach to newly diagnosed patients with MCL depends on the patient's eligibility for stem cell transplantation (SCT). Those who are eligible are usually treated with either rituximab-CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) followed by SCT or high dose cytarabine or other regimens such as HyperCVAD (cyclophosphamide, vincristine, doxorubicin, decadron, cytarabine, and methotrexate). The purine nucleoside analogues also have activity as single agents and with rituximab. Unfortunately none of these approaches can definitively cure patients with MCL, and new agents are needed.

In 2006, Velcade (bortezomib) was approved in the United States for use in patients with MCL who have had at least 1 prior treatment. Bortezomib was approved on the basis of data from 155 patients in 1 single-group phase 2 study because it demonstrated objective response benefits. The ORR was 33% and patients with response had a median duration of response of 9.2 months, and updated results report a median OS of 23.5 months for this single arm study.

In the EU there are no approved treatments for relapsed MCL. However, there are a number of cytotoxic medicinal agents that are approved for Non-Hodgkin Lymphoma in general or for indolent Non-Hodgkin Lymphoma, including anthracycline, alkylating agents, vinca alkaloids, antimetabolites etc. Many different single-agent treatments are in use for patients who have received prior treatment with an alkylating agent, an anthracycline, and rituximab, individually or in combination. Currently no single-agent treatment is consistently used or considered superior for the treatment of relapsed MCL.

Non-Clinical aspects

N/A

Clinical aspects

GCP compliance

According to the MAH all studies were conducted in accordance with the ethical requirements of Directive 2001/20/EC and with the ICH E6 guideline on Good Clinical Practice and the principles set forth in the Declaration of Helsinki.

- Clinical Pharmacology

Pharmacokinetics

Introduction

In support of this application for the use of temsirolimus IV in patients with MCL, an integrated population PK analysis of temsirolimus was provided in CSR-70829. The analysis combined PK data obtained from studies 3066K1-124-US, -145-US, -200-US, -203-EU (all previously submitted for the RCC marketing authorisation application (MAA)) and the pivotal MCL study -305-WW, and included concentration measurements from 1342 whole blood or plasma samples from 150 subjects for

temsirolimus and from 1648 samples from 279 subjects for sirolimus. The MCL population represented 40% and 24.2% of the total subjects in the population PK datasets for temsirolimus and sirolimus, respectively, and the blood sampling typically spanned study weeks 3 to 6. Furthermore, an additional completed phase 1/2 dose-escalation study of temsirolimus in combination with sunitinib (study 3066K1-402-WW), and an updated progress report on safety in 1 ongoing study in paediatric patients (study 3066K1-139-US) was provided (see Table 8). A progress report for 1 additional ongoing study in subjects with cancer who had hepatic impairment (NCI protocol 6813, Wyeth study 3066K1-152-US) was previously provided in support of the RCC MAA.

In vitro studies have demonstrated that single-agent temsirolimus exhibits important antitumour activity. Sirolimus, which is a major metabolite of temsirolimus following IV treatment, was also shown to have antitumour activity. The appearance of appreciable levels of sirolimus in the circulation of subjects with cancer therefore provided a rationale to derive a composite metric of drug exposure that described the algebraic sum of the areas under the concentration-time curve (AUC_{sum}) for both entities. Although temsirolimus and sirolimus share some common biological properties, substantial differences in the profile of activity and side effects can be obtained with differences in dose level, dose schedule, or route of administration.

The proposed treatment regimen for patients with MCL is 175 mg IV weekly for 3 weeks followed by weekly 75-mg IV doses. The comparative PK parameters described below were determined using the typical values and variance terms for clearance and volume of distribution terms from the integrated population PK analysis. Since blood sampling in the subjects with MCL was sparse in nature, data pooling of PK values was not performed.

Methods

- **Analytical methods**

Temsirolimus and its major metabolite sirolimus were assayed in blood and plasma using a combined HPLC/MS/MS assay in which both temsirolimus and sirolimus were simultaneously measured. This assay was split into 2 methods to quantify 2 differing concentration ranges (i.e., low range 0.25-25 ng/ml, and high range 2.5-2500 ng/ml). A cross-validation of this combined method with the previous separate temsirolimus and sirolimus assays, which were used for earlier PK studies, was conducted. The methods were sufficiently validated. Accuracy (% bias) and precision (% coefficient of variation) were reported at low, mid and high QC levels, and were within generally accepted ranges.

- **Pharmacokinetic data analysis**

Population PK analysis

Pharmacokinetic data from the final models of the previous mechanistic integrated analysis (CSR-64107) were merged with data from subjects with MCL (Study 3066K1-305-WW) in Study CSR-70829. Studies included in the population PK analysis CSR-70829 are presented in Table 1.

Table 1: Studies included in population PK analysis CSR-70829

Study Number	Study Description	Number Enrolled	IV Dose Range
Clinical Pharmacology Studies in Healthy Subjects			
3066K1-145-US[a]	Phase 1, open-label study to quantify the temsirolimus exposure/response relationship using S6 ribosomal protein in blood.	30	1 to 25 mg
Clinical Studies with a Clinical Pharmacology Component in Subjects with Cancer			
3066K1-124-US[a]	Phase 1, open-label, dose-escalation combination study with IFN to determine MTD in subjects with advanced RCC.	71	5 to 25 mg
3066K1-200-US[a]	Phase 2, randomized, blinded, parallel-group, dose-ranging study for efficacy, safety, and population PK in subjects with advanced RCC.	111	25, 75, 250 mg
3066K1-203-EU[a]	Phase 2, randomized, open-label, parallel-group, dose-ranging study to evaluate efficacy, safety, and population PK in subjects with advanced or metastatic breast cancer.	109	75, 250 mg
3066K1-305-WW	Phase 3, randomized, open-label, parallel-group, pivotal study to evaluate efficacy and safety in subjects with relapsed or refractory MCL.	162	175 and 75 mg, 175 and 25 mg

[a] Final data were presented in the previous MAA for RCC. Data from these studies are included in population PK analyses in this MAA.

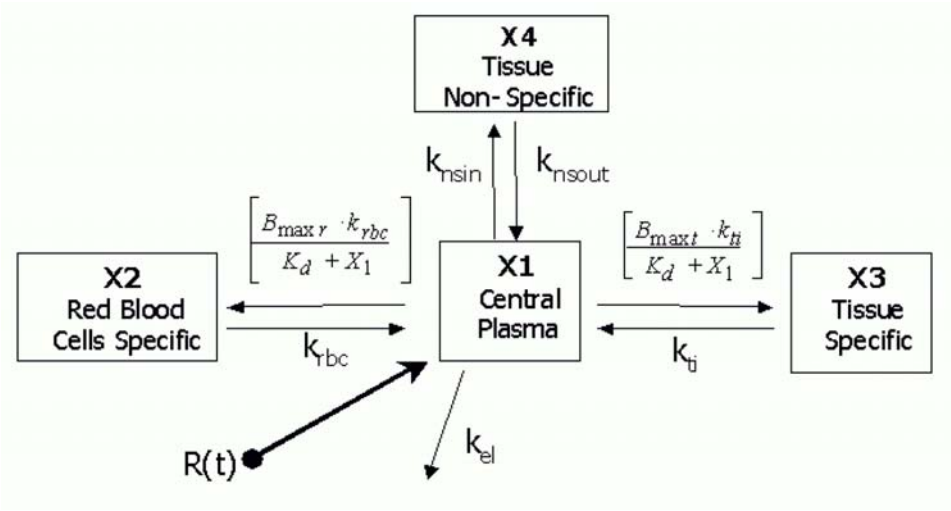
A summary of the comparison of the previous CSR-64107 and current population CSR-70829 PK data set is provided in Table 2.

Table 2: Comparison of the number of subjects and observations included in integrated population PK analyses CSR-64107 and CSR-70829

Analyte	Subgroup	N Integrated analysis from CSR-64107	Integrated analysis CSR-70829, with data from Study 305	Change (%)
Temsirolimus	Subjects	90	150	+67%
	Observations	1153	1342	+16%
Sirolimus	Subjects	211	279	+32%
	Observations	1312	1648	+25%

For the temsirolimus model, a nonlinear structure to describe both plasma and whole blood disposition, based on Study 3066K1-145-US of temsirolimus with healthy subjects, was applied. This model utilized 4 compartments in which specific, saturable distribution of temsirolimus to 2 of 3 peripheral compartments (blood cells and peripheral tissue) was described. The linear, 2-compartment model with first-order formation was applied to characterize sirolimus concentrations in blood. The same mechanistic model was used in current CSR-70829 as in the previous CSR-64107 (Figure 1). The final model for temsirolimus was based a data set of 1342 observations for 150 subjects.

Figure 1: PK model of temsirolimus (Study CSR-70829)



A linear, 2-compartment model with first-order formation was applied to characterize sirolimus concentrations in blood. The final model for sirolimus was based a data set of 1648 observations for 279 subjects.

The temsirolimus model was validated using goodness of fit and residual plots. Simulation yielded good predictability in plasma and blood. The sirolimus model was validated using diagnostic plots and a bootstrap approach.

Results

The results of the Final population PK model indicate that patients with MCL from study 3066K1-305-WW and patients with breast cancer from study 3066K1-203-EU yielded different temsirolimus CL values as compared to the other studies of the analysis.

The expanded relationship of temsirolimus CL for the typical patient was:

TVCL (L/h) = 112 * [1 + FLG1*(-0.178) + FLG2*(- 0.443)]

in which TVCL denotes typical value for CL; FLG1 = 1 for subjects with breast cancer in study 3066K1-203-EU and FLG1 = 0 for other; and FLG2 = 1 for subjects with MCL in study 3066K1-305-WW and FLG2 = 0 for other. Thus, for subjects without MCL (and without breast cancer), CL for the typical patient was 112 L/h, and for subjects with MCL (and without breast cancer), CL was 62.4 L/h. Other parameters were unaffected by covariate effects.

The effect of this reduced clearance in MCL patients was visualized using a Monte Carlo simulation of the final model. Based on this simulation, an increase of temsirolimus in blood was apparent in MCL patients, as compared to a typical patient without MCL (see Table 3).

The expression for sirolimus apparent clearance from whole blood was:

TVCL (L/h) = 15.5 · (DOSE/25000)0.172 · (1 – 0.0082 · DNUM) · (WT/75.5)-0.354 [3]

in which TV denotes typical value for CL; DOSE = temsirolimus dose in micrograms; DNUM = flag variable for dose (0 = single, 1 = multiple); and WT = body weight in kg. Other factors for sirolimus were also reported that included effect of study protocol (study 145 or study 124) on central volume of distribution.

Absorption

Based on data obtained by the population PK model, after treatment of MCL patients with 175/75 mg IV doses, the temsirolimus model-predicted peak concentration (C_{max}) in whole blood were 2457 ng/ml and 2574 ng/ml at week 1 and week 3. These values are 28.3% higher at week 1 and 43.7% higher at week 3, compared with predicted C_{max} values for the typical subject without MCL (see Table 3). This increase in MCL patients as compared to patients without MCL was caused by the decreased clearance in MCL patients (see section *'excretion'*). In MCL patients receiving the 175/75 mg IV doses, model-predicted median (minimum, maximum) AUC for temsirolimus was 885 (327, 2752) ng.h/mL and for sirolimus was 2602 (976, 5929) ng.h/ml.

Table 3. Comparative PK exposure of temsirolimus in the typical subject with and without MCL(CSR-70829)

	Subjects Without MCL	Subjects With MCL
Temsirolimus		
Week 1 C_{max} in blood (ng/mL)	1915 (907, 3805)	2457 (1112, 5303)
Week 3 C_{max} in blood (ng/mL)	1791 (859, 4218)	2574 (1155, 6267)
Week 6 C_{trough} in blood (ng/mL)	0.148 (0.011, 2.299)	1.19 (0.068, 15.4)

Data represented as median (10th, 90th percentile) concentrations in units of ng/ml. Treatment was temsirolimus 175 mg IV once weekly for 3 weeks, following by weekly doses of 75 mg.

The disposition of sirolimus was not affected by the presence or absence of MCL.

Distribution

Information on distribution of IV temsirolimus was previously described in the RCC MAA. No additional information on the distribution of temsirolimus is available at this time.

Elimination

- **Excretion**

Information on the elimination of IV temsirolimus was previously described in the RCC MAA, indicating a clearance from blood of 11.4 ± 2.4 l/h. Based on data from the population PK CSR-70829, for the typical subject (75.5 kg), mean values for clearance from plasma were 62.4 L/h in subjects with MCL versus 112 L/h in subjects without MCL. Due to this lower clearance in patients with MCL, temsirolimus C_{trough} in whole blood at end of week 6 was 1.19 ng/mL in subjects with MCL versus 0.148 ng/mL in subjects without MCL (see Table 3).
For sirolimus, clearance in MCL patients was not significantly different from that in patients without MCL. A moderate effect of body weight on sirolimus clearance was noted (See section *'Special population – weight'*).
Since sirolimus clearance is not different for patients with and without MCL, sirolimus trough levels were comparable in these two subgroups of patients. Sirolimus trough levels at week 6 were estimated as 10.7 ng/ml.

- **Metabolism**
- **Inter-conversion**
- **Pharmacokinetics of metabolites**
- **Consequences of possible genetic polymorphism**

Information on metabolism, interconversion, PK of metabolites, and consequences of genetic polymorphism of IV temsirolimus was previously described in the RCC MAA. No additional information on the distribution of temsirolimus is available at this time.

Dose proportionality and time dependency

- **Dose proportionality**

As indicated in the RCC MAA, temsirolimus C_{max} and AUC increase with increasing dose in a less than proportional manner. This non-linear PK is believed to be due to saturable binding of temsirolimus to FKBP-12 in blood cells and peripheral tissues, leaving relatively more temsirolimus available for clearance at higher doses.

Pharmacokinetics in target population

The additional data included in this Application are obtained from MCL patients.

Special populations

Intrinsic factors of PK variability were tested as part of the integrated population PK analysis in CSR-70829.

- **Impaired renal function**

No effect of renal impairment was previously indicated in the RCC MAA. Additional data obtained in this MCL application from covariate assessment in the population PK report CSR-70829 confirm no significant differential effects for creatinine clearance.

- **Impaired hepatic function**

Initial safety and PK data on subjects with varying degrees of hepatic impairment were provided in the RCC MAA. In an ongoing NCI/CTEP study (NCI protocol 6813, Wyeth study 3066K1-152-US), dose-limiting toxicity events of grade 3 or higher thrombocytopenia were identified. However, current data are insufficient to draw any definitive conclusions related to the PK association to toxicity in patients with hepatic impairment. This lack of definitive data notwithstanding, to mitigate the risk for toxicity in patients with MCL, section 4.4 of the SPC has been updated with a warning in order to recommend that temsirolimus be used with caution in patients with hepatic impairment. The SPC further states that the use of temsirolimus in patients with severe hepatic impairment is not recommended. In addition, section 4.2 of the SPC has been updated to highlight that use of temsirolimus in patients with moderate (total bilirubin greater than 1.5-3 times upper limit of normal [ULN] and any AST greater than ULN) or severe (total bilirubin greater than 3 times ULN and any AST greater than ULN) hepatic impairment is not recommended.

Further, the MAH has committed to provide additional PK data from patients with hepatic impairment as a post-authorisation follow-up measure for review by CHMP.

- **Gender**
- **Race**

No effect of gender and race was previously indicated in the RCC MAA. Additional data obtained in this MCL application from covariate assessment in the population PK CSR-70829 indicated no significant differential effects for gender or race.

- **Weight**

The disposition of temsirolimus was not affected by weight. However, for sirolimus, clearance was reduced at increased weight, and the extremes of body weight from the population PK dataset were shown to alter C_{trough} values, as shown in Table 4.

Table 4. Comparative exposure of sirolimus in the typical subject with varying body weight (CSR-70829)

	Minimum BW (38.7 kg)	Median BW (75.5 kg)	Maximum BW (158.9 kg)
Week 3 C_{trough}	16.7 (7.59, 34.3)	22.2 (11.4, 42.0)	32.9 (17.5, 56.9)
Week 6 C_{trough}	8.28 (3.54,19.3)	10.7 (4.82, 21.7)	16.7 (8.47, 38.2)

Data represented as median (10th, 90th percentile) concentrations in units of ng/ml. Treatment was 175 mg IV once weekly for 3 weeks followed by weekly doses of 75 mg.

- **Elderly**

The results from covariate assessment in the population PK Study CSR-70829 indicated no significant differential effects for age. In the previous RCC MAA, the effect of age on temsirolimus PK has been investigated up to an age of 79 years. Age did not appear to affect temsirolimus and sirolimus PK significantly.

- **Children**

A phase 1/2 study in paediatric patients with cancer (3066K1-139-US) is currently being conducted, and an updated interim report was provided by the applicant.
This is an open-label, 2-part study. Part 1 was a dose-escalation study designed to establish the MTD or a biologically effective dose of temsirolimus. The starting dose was 10 mg/m^2, and the dose was increased to 25, 75, and 150 mg/m^2. Sequential cohorts of subjects (paediatric and adolescent subjects aged 1 to 21 years) were enrolled at each dose level.
Based on the interim analysis for this study, clearance of temsirolimus from blood appears lower and AUC is higher in the paediatric population as compared to adults. However, exposure to sirolimus is reduced in paediatric patients, and the resulting total temsirolimus + sirolimus exposure, as measured by AUC_{sum} is comparable to that in adults. These findings collectively suggest that the paediatric population is not at risk for excessive exposure to temsirolimus-related active moieties.
Still, the MTD in the paediatric population of 150 mg/m^2, and the further investigated dose appear lower than in the adult population, where in Study 3066K1-101-EU the 220 mg/m^2 dose was considered the MTD.
This study will be assessed in detail when the final study report is provided. At this stage, based on the interim study report, it is concluded that the paediatric population is not at risk of excessive exposure to temsirolimus and sirolimus. Final recommendations on the use of temsirolimus in the paediatric population will be considered for inclusion in the SPC upon completion of part 2 of this study.

Interactions

Information on drug interactions of temsirolimus was previously provided in the RCC MAA for subjects receiving the 25-mg IV weekly dosage regimen. The proposed treatment regimen for patients with MCL uses higher doses than that for patients with RCC.

Inhibition of CYP3A4
Information was provided in the RCC MAA, demonstrating that sirolimus exposures (AUC) increased approximately 3.1-fold after concomitant administration of 25 mg IV temsirolimus with ketoconazole, a cytochrome P450 (CYP)3A4 inhibitor, compared with temsirolimus treatment alone. Considering that the dose proposed for patients with MCL (175 mg once weekly for 3 weeks followed by weekly doses of 75 mg) is higher and the regimen is different from that defined for patients with RCC (25 mg once weekly), it is recommended that coadministration of strong CYP3A4 inhibitors with temsirolimus to patients with MCL be avoided. This warning is included in the SPC, section 4.4, Special warnings and precautions for use.

Induction of CYP3A4
Information was provided in the RCC MAA demonstrating that sirolimus exposures (AUC) decreased by 56% when given concomitantly with rifampicin, a CYP3A inducer, compared with temsirolimus treatment alone. Considering that the dose proposed for patients with MCL (175 mg once weekly for 3 weeks followed by weekly doses of 75 mg) is higher and the regimen somewhat different from that defined for patients with RCC (25 mg once weekly), it is recommended that coadministration of

CYP3A4/5 inducers with temsirolimus to patients with MCL be avoided. This warning is included in the SPC, section 4.4, Special warnings and precautions.

Inhibition of CYPs by temsirolimus and sirolimus

Data were also provided in the RCC MAA, demonstrating that temsirolimus 25 mg IV did not alter the disposition of desipramine, a CYP2D6 substrate. No additional data on the potential for drug interaction applying the higher temsirolimus dose are available at this time.

For information purpose, the *in vitro* Ki of temsirolimus, as obtained in Study RPT-45792 are provided in Table 5.

Table 5: K_i values of temsirolimus for CYP isoforms (RPT-45792)

Isoform tested	Temsirolimus K_i (μM)	Temsirolimus C_{max}/K_i ratio[a]
CYP3A4/5	3.1	0.80
CYP2D6	1.5	1.65
CYP2C9	14	0.18
CYP2C8	27	0.09

[a] C_{max} following 175-mg IV temsirolimus dose. K_i values assume C_{max} of 2574 ng/ml (2.47 μM) (Study CSR-70829).

Inhibition of CYP2D6 and 3A4 by temsirolimus is not yet considered sufficiently investigated. With the current treatment, applying the 175/75 mg dose, the C_{max} after 3 weeks of treatment, as estimated based on the population PK model in CSR-70829, is 2574 ng/ml. By applying this C_{max} level, it is clear that the potential for clinically relevant inhibition of CYP3A4 and 2D6 at this dose *in vivo* is much higher (C_{max}/K_i is 0.80 and 1.65 for CYP3A4 and CYP2D6, respectively, see Table 5) than that for the 25 mg dose, where temsirolimus C_{max}/K_i of 0.19 and 0.38 were found for CTYP3A4 and 2D6, respectively. Only a CYP2D6 *in vivo* DDI study, applying a temsirolimus dose of 25 mg, was conducted so far. Although based on that study, it was concluded that no clinically relevant inhibition of either CYP2D6 or 3A4 occurs at a temsirolimus dose of 25 mg for RCC, this can not be concluded yet for the higher dose of 175/75 mg for MCL.

The MAH has committed to conduct an *in vivo* interaction study with desipramine and to provide the final clinical study report for review by CHMP following the completion of the study. This study is planned to be conducted in MCL patients, and in case a relevant interaction is observed, an additional DDI study with CYP3A4 substrates will be initiated.

Exposure relevant for safety evaluation

Based on simulations by the population PK model in CSR-70829, the estimated temsirolimus C_{max} is 2575 ng/ml. Estimated AUC for temsirolimus was 885 ng.h/mL and for sirolimus 2602 ng.h/ml.

Discussion on Pharmacokinetics

The pharmacokinetics of temsirolimus and sirolimus in MCL patients after IV treatment with 175/75 mg temsirolimus was investigated using a population PK model. The model provided data related to nonlinear exposure, covariate effects, and comparative measures of exposure to be compared with other non-MCL patients. Simulations conducted using this model indicated that subjects with MCL exhibited a 44% lower clearance of temsirolimus from plasma compared to subjects without MCL. The difference in temsirolimus clearance resulted in increases in temsirolimus C_{max} and C_{trough} compared with subjects without MCL. No changes in sirolimus apparent clearance in MCL patients as compared with other patients were found. The contribution of temsirolimus to the concentrations of active moieties at the end of the dosage interval is considered to be modest.
Body weight increasing from 38.7 kg to 158.9 kg was shown to exert a modest reduction of sirolimus apparent clearance that translated to an almost 2-fold range in C_{trough} values of sirolimus.

Treatment differences in the temsirolimus-containing regimens for MCL were associated with differences in drug exposure. For subjects receiving the 175/75 mg doses, mean AUC of temsirolimus and sirolimus were 3-fold and 2.5 fold higher, respectively, than these values after the 175/25 mg regimen.

A study investigating the effect of hepatic impairment is ongoing, and only an interim report is available yet. This lack of definitive data notwithstanding, to mitigate the risk for toxicity in patients with MCL, section 4.3 of the SPC has been updated to include a contraindication in MCL patients with moderate or severe hepatic impairment and section 4.4 of the SPC with a corresponding warning. In addition, section 4.2 of the SPC has been updated to highlight that use of temsirolimus in patients with moderate (total bilirubin greater than 1.5-3 times upper limit of normal [ULN] and any AST greater than ULN) or severe (total bilirubin greater than 3 times ULN and any AST greater than ULN) hepatic impairment is not recommended.

The lack of data in hepatically impaired patients was previously considered acceptable for the RCC 25 mg dose. However, considering the increased dose of 175/75 mg in MCL patients, with more profound AEs, in addition to the increased exposure indicated in the interim report of the hepatic impairment study in hepatically impaired patients, it is considered not enough to only warn for the use in patients with hepatic impairment. In this regard, the MAH has committed to provide the final results of the completed hepatic impairment study and to provide concomitant dose advice for patients with various stages of hepatic impairment as a follow-up measure for review by CHMP.

The proposed warnings on inhibitors and inducers of CYP3A4 are agreed. However, inhibition of CYP2D6 and 3A4 by temsirolimus is not yet considered sufficiently investigated. With the current treatment, applying the 175/75 mg dose, the C_{max} after 3 weeks of treatment, as estimated based on the population PK model in CSR-70829, is 2574 ng/ml. By applying this C_{max} level, it is clear that the potential for clinically relevant inhibition of CYP3A4 and 2D6 at this dose *in vivo* is much higher (C_{max}/K_i is 0.80 and 1.65 for CYP3A4 and CYP2D6, respectively) than that for the 25 mg dose, where temsirolimus C_{max}/K_i of 0.19 and 0.38 were found for CTYP3A4 and 2D6, respectively. Only a CYP2D6 *in vivo* DDI study, applying a temsirolimus dose of 25 mg, was conducted so far. Although based on that study, it was concluded that no clinically relevant inhibition of either CYP2D6 or 3A4 occurs at a temsirolimus dose of 25 mg for RCC, this can not be concluded yet for the higher dose of 175/75 mg for MCL.

The MAH has committed to conduct an *in vivo* drug interaction study with desipramine and to provide the final clinical study report for review by CHMP following the completion of the study. This study is planned to be conducted in MCL patients, and in case a relevant interaction is observed, an additional DDI study with CYP3A4 substrates will be initiated.

Overall, by applying population PK modelling, the applicant has demonstrated that the temsirolimus exposure in MCL patients is increased as compared to non-MCL patients. Two FUMs have been agreed; one related to hepatically impaired patients and one related to the possible inhibition of CYP2D6 and 3A4 by temsirolimus. The MAH has committed to provide the requested data within agreed timeframes for review by CHMP.

Pharmacodynamics

Mechanism of action

No new data were provided for this application. Current knowledge on the mechanism of action is summarized in the introduction above.

Primary pharmacology

The effects of temsirolimus on the phosphorylation state of key proteins in the mammalian target of rapamycin (mTOR) pathway in tumour tissue, and transitional zone tissue were investigated in Study 3066K1-147-US.

The secondary objectives of this study were:
· To evaluate the effects of temsirolimus on global and targeted gene and/or protein expression patterns in the PBMCs;
· To evaluate the effects of temsirolimus on global and targeted gene expression patterns in the tumour tissue and transitional zone tissue;
· To compare the effects of temsirolimus in PBMCs and the tumour tissue in an attempt to identify surrogate markers of temsirolimus activity and to determine if blood can be used as a surrogate tissue source for biomarkers of drug activity in the tumour.

Methods
Study 3066K1-147-US was an open-label, exploratory, biomarker study of IV temsirolimus given to subjects with newly diagnosed, advanced-stage head and neck cancer. Sixteen (16) subjects were enrolled in the study. Subjects were to receive 25 mg of IV temsirolimus once weekly for 3 weeks before beginning other therapy appropriate for their cancer. Subjects remained in the follow-up period for approximately 2 weeks after the last dose of temsirolimus.
Tumour biopsies and adjacent transitional zone and adjacent normal tissue (if available) were obtained for biomarker analyses at screening. A second set of tissue samples was obtained approximately 1 to 7 days after the third dose of temsirolimus. For those subjects undergoing subsequent surgery as part of their appropriate cancer therapy, tissue samples were also obtained at the time of surgical resection. Whole blood samples were collected at screening, 1 to 7 days after the third dose of temsirolimus, and at the final visit for determination of temsirolimus and sirolimus levels and for pharmacodynamic (PD) and pharmacogenomic analyses.

Results
The results of comparisons of levels of selected proteins (unphosphorylated and phosphorylated) in the mTOR signalling pathway in tissue samples before and after treatment with temsirolimus are summarized in Table 6 and Table 7 for the evaluable and safety populations, respectively.
The evaluable population included 10 patients who received at least 3 doses of temsirolimus and provided at least 1 pre-administration and at least 1 post-administration blood and tumour tissue samples, which enabled a pairwise comparison to be performed.
The analysis on the safety population utilized all available data from the 16 patients treated in the study. Pre therapy protein levels were determined using samples provided at the screening visit; post therapy levels were based on samples provided at day X (1 to 7 days after the third dose) or at the final visit. The analysis of protein levels in PBMCs was not performed because only post therapy samples were available.

Table 6. Pharmacodynamic markers - Summary of data by protein and tissue and comparisons between posttherapy and pretherapy measurements: Evaluable population (n=10)

Protein	Tissue	Time Point	N	Mean	SD	p-Value[a] (Posttherapy vs PreTherapy)
S6	Adjacent Normal	Pre-Therapy	3	0.375	0.610	
		Post Therapy	3	0.126	0.203	0.618
	Transitional Zone	Pre-Therapy	4	0.829	0.337	
		Post Therapy	4	1.004	0.668	0.395
	Tumor	Pre-Therapy	10	1.298	0.650	
		Post Therapy	10	0.472	0.445	0.003
pS6	Adjacent Normal	Pre-Therapy	4	2.256	0.600	
		Post Therapy	4	0.670	0.555	0.008
	Transitional Zone	Pre-Therapy	4	1.695	0.825	
		Post Therapy	4	0.626	0.639	0.017
	Tumor	Pre-Therapy	10	1.396	0.775	
		Post Therapy	10	0.186	0.276	<.001
4EBP1	Adjacent Normal	Pre-Therapy	1	0.383	N/S	
		Post Therapy	1	0.018	N/S	.
	Transitional Zone	Pre-Therapy	1	1.058	N/S	
		Post Therapy	1	1.309	N/S	.
	Tumor	Pre-Therapy	7	1.716	0.957	
		Post Therapy	7	1.159	1.011	0.031
p4EBP1	Adjacent Normal	Pre-Therapy	3	2.053	2.229	
		Post Therapy	3	1.221	1.188	0.500
	Transitional Zone	Pre-Therapy	4	2.038	1.788	
		Post Therapy	4	2.891	3.545	0.640
	Tumor	Pre-Therapy	10	2.289	1.249	
		Post Therapy	10	1.491	1.350	0.059
eIF4E	Adjacent Normal	Pre-Therapy	2	1.118	0.639	
		Post Therapy	2	0.883	0.110	.
	Transitional Zone	Pre-Therapy	2	1.441	0.468	
		Post Therapy	2	1.669	0.549	.
	Tumor	Pre-Therapy	9	1.253	0.686	
		Post Therapy	9	1.064	0.483	0.283
p-eIF4E	Tumor	Pre-Therapy	2	0.526	0.404	
		Post Therapy	2	0.369	0.281	.
Cyclin D1	Transitional Zone	Pre-Therapy	1	0.474	N/S	
		Post Therapy	1	0.023	N/S	.
	Tumor	Pre-Therapy	1	0.229	N/S	
		Post Therapy	1	0.051	N/S	.
Akt	Adjacent Normal	Pre-Therapy	2	1.171	0.013	
		Post Therapy	2	0.656	0.119	.
	Transitional Zone	Pre-Therapy	1	0.850	N/S	
		Post Therapy	1	0.550	N/S	.
	Tumor	Pre-Therapy	8	1.285	0.708	
		Post Therapy	8	0.879	0.226	0.109
p-Akt	Adjacent Normal	Pre-Therapy	2	0.485	0.686	
		Post Therapy	2	0.515	0.728	.
	Transitional Zone	Pre-Therapy	2	0.482	0.294	
		Post Therapy	2	0.233	0.137	.
	Tumor	Pre-Therapy	9	0.584	0.367	
		Post Therapy	9	0.438	0.378	0.013

Table 7. Pharmacodynamic markers: Summary of data by protein and tissue and comparisons between posttherapy and pretherapy measurements: Safety population (n=16)

Protein	Tissue	Time Point	n	Mean	SD	p-Value[a] (Posttherapy vs Pretherapy)
S6	Adjacent Normal	Pretherapy	7	1.882	3.507	
		Posttherapy	5	1.391	2.098	0.833
	Transitional Zone	Pretherapy	8	2.422	3.373	
		Posttherapy	6	0.721	0.685	0.542
	Tumor	Pretherapy	14	1.757	1.488	
		Posttherapy	14	0.888	1.134	0.002
pS6	Adjacent Normal	Pretherapy	7	2.320	0.500	
		Posttherapy	6	1.147	0.877	0.019
	Transitional Zone	Pretherapy	8	2.080	1.068	
		Posttherapy	6	0.717	0.717	<0.001
	Tumor	Pretherapy	14	1.574	0.715	
		Posttherapy	14	0.539	0.681	<0.001
4EBP1	Adjacent Normal	Pretherapy	3	2.097	2.263	
		Posttherapy	2	1.595	2.230	.
	Transitional Zone	Pretherapy	5	1.922	2.114	
		Posttherapy	3	1.959	0.721	0.229
	Tumor	Pretherapy	11	1.881	1.259	
		Posttherapy	11	1.743	1.361	0.562
p4EBP1	Adjacent Normal	Pretherapy	5	1.619	1.804	
		Posttherapy	4	2.118	2.039	0.964
	Transitional Zone	Pretherapy	8	1.791	1.446	
		Posttherapy	6	2.411	2.916	0.520
	Tumor	Pretherapy	14	2.131	1.121	
		Posttherapy	14	1.694	1.348	0.259
eIF4E	Adjacent Normal	Pretherapy	6	0.700	0.655	
		Posttherapy	5	1.418	1.418	0.926
	Transitional Zone	Pretherapy	6	0.936	0.451	
		Posttherapy	4	1.147	0.707	0.485
	Tumor	Pretherapy	13	1.131	0.646	
		Posttherapy	13	0.926	0.458	0.137
p-eIF4E	Tumor	Pretherapy	2	0.526	0.404	
		Posttherapy	2	0.369	0.281	.
p53	Adjacent Normal	Posttherapy	1	0.945	N/S	.
	Transitional Zone	Pretherapy	1	0.005	N/S	.
	Tumor	Pretherapy	1	2.007	N/S	
		Posttherapy	1	0.000	N/S	.
Cyclin D1	Transitional Zone	Pretherapy	1	0.474	N/S	
		Posttherapy	1	0.023	N/S	.
	Tumor	Pretherapy	1	0.229	N/S	
		Posttherapy	1	0.051	N/S	.
Akt	Adjacent Normal	Pretherapy	4	1.037	0.161	
		Posttherapy	2	0.656	0.119	.
	Transitional Zone	Pretherapy	2	0.820	0.043	
		Posttherapy	2	0.795	0.346	.
	Tumor	Pretherapy	10	1.339	0.765	
		Posttherapy	10	0.925	0.228	0.081
p-Akt	Adjacent Normal	Pretherapy	4	0.681	0.715	
		Posttherapy	3	0.420	0.540	0.547
	Transitional Zone	Pretherapy	4	0.533	0.182	
		Posttherapy	3	0.309	0.164	0.071
	Tumor	Pretherapy	12	0.535	0.339	
		Posttherapy	12	0.426	0.324	0.062

Based on analysis of the evaluable population, there were nominally significant differences (p-value <0.05) between protein levels at screening and after treatment with temsirolimus for several of the proteins evaluated. In tumour tissue samples, there were significant decreases in the levels of S6 ribosomal protein, both unphosphorylated (S6) and phosphorylated (pS6) (p-values 0.003 and <0.001, respectively); 4EBP1 (p-value 0.031) and pAKT (p-value 0.013). There were also significant

decreases in the level of pS6 in transitional zone tissue (p-value 0.017) and normal tissue adjacent to the tumour (p-value 0.008).
Based on analysis of all available samples, there were only nominally significant differences between the protein levels at screening and after treatment with temsirolimus for S6 ribosomal protein. In tumour tissue samples, there was a significant decrease in the level of both S6 and pS6 after treatment with temsirolimus (p-values 0.002 and <0.001, respectively). pS6 levels also decreased significantly in samples of transitional zone tissue (p-value <0.001) and normal tissue adjacent to the tumour (p-value 0.019).
Thus, exposure to temsirolimus may be associated with decreased levels of pS6 and S6, 4EBP1, and pAKT.

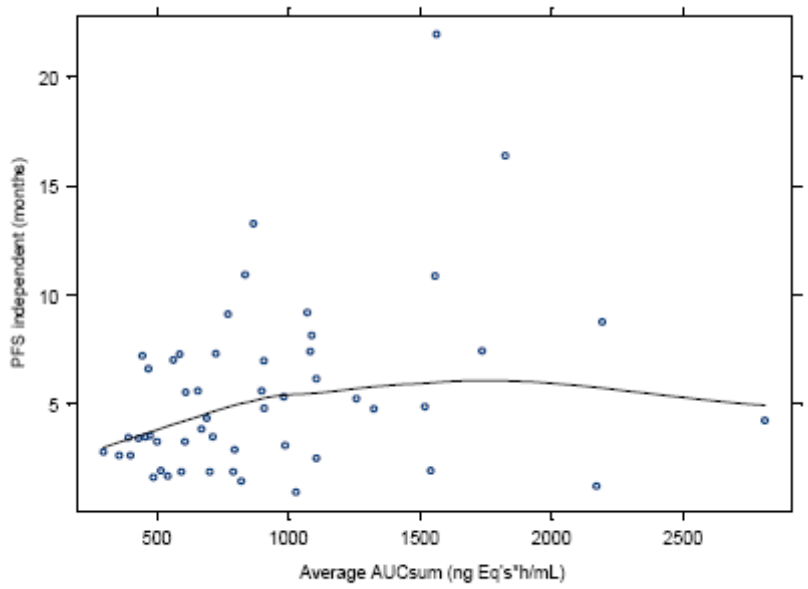
This study provides exploratory information on biomarkers which may be pursued in future clinical studies with temsirolimus. Since PBMC cells were not analysed in this study, it was not possible yet to identify surrogate markers of temsirolimus activity and to determine if blood can be used as a surrogate tissue source for biomarkers of drug activity in the tumour.
These data have no impact on the current application for MCL.

Secondary pharmacology

Intrinsic factors of PK variability were also tested as part of the integrated population PK analysis CSR-70829. The results from covariate assessment in this study indicated no significant differential effects for clinical laboratory endpoints, including alanine aminotransferase, aspartate aminotransferase, hematocrit, total bilirubin, or creatinine clearance.

Relationship between plasma concentration and effect
An analysis of the association between drug exposure and clinical response in 52 subjects with MCL from study 305 was examined using the derived, individual predicted values for the sum of temsirolimus and sirolimus AUC values, uncorrected for differences in molecular weight (AUCsum) and average maintenance dose based on subject dose history (Figure 2). The individual subject average AUCsum values were then related to the given subject's independent assessment of PFS. Graphically, the data indicated that there was no clear correlation between average AUC_{sum} and PFS.

Figure 2. Duration of progression-free survival vs. individual predicted average AUC_{sum} after temsirolimus IV treatment in subjects with MCL in Study 306K1-305-WW (CSR-70829)



Data trend shown using Loess function [a]

The exposure–response profile of temsirolimus IV described from study 3066K1-145-US provided proof of modulation of the biochemical target in humans. This study also provided a minimum dosage of 12.4 mg that would be needed to ensure optimal distribution of temsirolimus to the periphery. In this light, the dosing regimen of 175/75 mg appears high. However, according to the applicant, for oncology indications, higher intensity dosage regimens have generally predominated, supported by non-clinical models that demonstrate a dose- or exposure-response relationship. For temsirolimus IV, the benefits of more intensive treatment regimens include the ability to exceed maximal specific but non-critical binding capacity, and to achieve enhanced drug distribution as compared with lower IV doses or alternate dose regimens. Response information demonstrates a trend of activity in PFS after the temsirolimus 175/25-mg treatment and significant improvement in PFS after the temsirolimus 175/75-mg treatment. These findings indicate that the growth of some neoplasms, such as MCL, by virtue of its unique pharmacological dependencies on mTOR signalling, appears to be particularly susceptible to anti-tumour activity when temsirolimus is administered at higher doses.

Discussion on pharmacodynamics

MCL is characterized by t(11;14) resulting in over expression of cyclin D1, a member of the phosphatidylinositol 3-kinase (PI3K) pathway. In MCL there is a rationale for development of temsirolimus, as the constitutively expression of cyclin D1 mRNA is potentially subject to translational regulation by a pathway involving the mammalian target of rapamycin (mTOR).

The MAH submitted limited additional pharmacodynamic data as part of this application. An exploratory phase 1/2 study indicated that exposure to temsirolimus may be associated with decreased levels of pS6 and S6, 4EBP1, and pAKT, in tumour and adjacent tissues. Since PBMCs were not analysed in this study, it was not possible yet to identify surrogate markers of temsirolimus activity in PBMCs and to determine if blood can be used as a surrogate tissue source for biomarkers of drug activity in the tumour. However, these data have no impact on the current application for MCL.

The applicant states that the high proposed dose for treatment of MCL is in line with the routinely higher dose-intensities applied in oncology. Still, the proposed 175/75 mg dose is much higher than the dose of 12.4 mg estimated to occupy all receptors and ensure distribution of temsirolimus to the periphery. Based on the results from the clinical comparison of the 175/75mg and 175/25 mg regimens (with a tendency for increased PFS at the higher dose), the applicant argues that this demonstrates that the higher dose is critical for MCL, probably due to importance of non-specific binding of temsirolimus. However, no clear relationship was observed between temsirolimus + sirolimus AUCsum and PFS. Moreover, no additional pharmacodynamic support for this high dose is provided either, i.e., no substantiation of any difference in this respect between RCC and MCL was provided, and pharmacokinetic support based on the model of the proposed non-specific binding is currently lacking. For the RCC indication, a much lower dose of 25 mg is applied. Thus, the high dose for the MCL indication is not yet considered sufficiently founded.

Therefore, upon request by the CHMP, the applicant has committed to conduct a randomised clinical study in patients with MCL to explore whether similar efficacy can be achieved with a less toxic dose regimen (see discussion on clinical efficacy and safety below). The MAH will provide these data within agreed timeframes for review by CHMP.

Clinical Efficacy

This application contains a final clinical study report of pivotal study 3066K1-305-WW, a final report of the population PK analysis (see above), final clinical study reports for a phase 1 biomarker study that was ongoing at the time of the MAA for RCC (study 3066K1-147-US), an additional completed phase 1/2 dose-escalation study of temsirolimus in combination with sunitinib (study 3066K1-402-WW), and an updated progress report on safety in 1 ongoing study in paediatric patients (study 3066K1-139-US) (Table 8).

Table 8 Studies submitted in the present type II variation application

Pivotal study	
Study 305	A phase 3 study in subject with relapsed and/or refractory MCL (study 3066K1-305-WW)
Other submitted studies in this application (other indications than mantle cell lymphoma)	
CSR-70829	Population pharmacokinetics
Study 147	A phase 1 study of temsirolimus in head and neck tumors evaluating potential biomarkers in this population (study 3066K1-147-US) (previously submitted; now final report)
Study 402	A phase I/II study of temsirolimus in combination with sunitinib (Study 3066K1-402-WW). This study was terminated early
Study 139	A phase I/II study in paediatric patients (study 3066K1-139-US). Ongoing

Selection of dose

To induce an early response, a temsirolimus starting dose of 175 mg weekly was administered for the first 3 weeks. According to the MAH, the temsirolimus dose of 175 mg was selected based on results in a phase 2 study of temsirolimus sponsored by the NCI CTEP (study N0186, Witzig TE, JCO 2005; 5347). In part 1 of study N0186, subjects with previously treated MCL were initially treated with temsirolimus 250 mg weekly. Repeated dose delays and reductions were required because of toxicities. The average dose in month 1 was approximately 175 mg for the subjects who responded to treatment. Most subjects had dose delays after the second dose of 250 mg. Therefore, a starting dose of 175 mg weekly was selected for the phase 3 study. Three (3) weeks of treatment at 175 mg was chosen based on the assumption that subjects would be likely to tolerate one more week at 175 mg than at 250 mg. Weekly doses of either 75 mg or 25 mg after the starting doses of 175 mg were also selected based on previous clinical experience in the N0186 study. The protocol was amended to explore a 25-mg dose to improve safety while maintaining efficacy. Observed response rates were similar to that observed with 250 mg weekly, but TTP appeared shorter with the 25-mg dose compared with the 250-mg dose (5.5 vs. 6.6 months). (Ansell S,M, et al *JCO* 2006: 7532) .
The 75-mg dose selected for study 3066K1-305-WW is an intermediate dose between 175 mg and 25 mg and closer to the lower end of the range that was tolerated in the N0186 study. Furthermore, the 75-mg dose has shown activity in other tumor types.
Temsirolimus at doses up to 250 mg has been tested in phase 2 studies. Doses of 25, 75, and 250 mg resulted in similar response rates in phase 2 studies of renal cell carcinoma (RCC; study 3066K1-200-US) and breast cancer (75- and 250-mg doses only; study 3066K1-203-EU), although the response rates were higher in MCL.

Pivotal study

In support for the extension of indication to include treatment of relapsed and/or refractory mantle cell lymphoma, the results of 1 completed phase 3 study in subjects with relapsed/refractory MCL (Study 3066K1-305-WW) was submitted.

Methods

This was a Phase 3, randomized, open-label, multicenter study. In total 162 patients were randomized into 3 arms, in a 1:1:1 ratio (A:B:C), in 108 centers in 15 countries. The 3 study arms are as follows:

- Arm **A**: Temsirolimus 175 mg IV q1week for 3 weeks; followed by 75 mg IV q1week (temsirolimus 175/75)
- Arm **B**: Temsirolimus 175 mg IV q1week for 3 weeks; followed by 25 mg IV q1week (temsirolimus 175/25)
- Arm **C**: Investigator's choice

"Investigator's Choice" as comparator was chosen because there is no single standard therapy for mantle cell lymphoma. There are many choices for single-agent treatment options for patients who have received 2 to 7 prior therapies with an alkylating agent and an anthracycline, and rituximab, individually or in combination, but none is clearly superior or consistently used. A list of the more

commonly used therapies was provided to the investigators to choose the most appropriate regimen, which included fludarabine, chlorambucil, gemcitabine, cyclophosphamide, cladribine, etoposide, prednisone, and dexamethasone.

For Arm A and B (temsirolimus) premedication with intravenous diphenhydramine 25 to 50 mg (or similar antihistamine) was to be administered approximately 30 minutes before the start of each temsirolimus infusion. Dose reductions were to be performed relating to hematotoxicity and non-hematologic toxicity.

Study Participants

Inclusion Criteria included:
1. Mantle Cell Lymphoma (MCL) confirmed with histology, immunophenotype, and cyclin D1 analysis.
2. Received 2 to 7 prior therapies, which may include haematopoietic stem cell transplant (i.e. induction + consolidation + maintenance).
3. Prior treatment with an alkylating agent and an anthracycline, rituximab, individually or in combination, and status that is at least one of the following:
    a. Primary disease refractory to at least 2 regimens
    b. Refractory to at least 1 regimen after first relapse
    c. Refractory or untreated after second or greater relapse
    d. Refractory to first line and relapsed after second line

Chemotherapy combinations may include, but are not limited to: CHOP, R-CHOP, FCM, R-FCM, ICE, DHAP, and hyper-CVAD.

Exclusion Criteria included:
1. Patients who are less than or equal to 6 months from allogeneic haematopoietic stem cell transplant and who are on immunosuppressive therapy or have evidence of graft versus host disease.
2. Prior investigational therapy within 3 weeks of first dose. Investigational therapy is defined as treatment that is not approved for any indication.
3. Active central nervous system (CNS) metastases, as indicated by clinical symptoms, cerebral edema, requirement for corticosteroids and/or progressive growth.
4. Active second malignancy that requires treatment or that would interfere with assessment of response of MCL.
5. History of any other primary malignancy with < 5 years documentation of a disease-free state. (May be discussed with Wyeth medical monitor, e.g. patients with a history of basal cell or squamous cell carcinomas of the skin or cervical carcinoma in situ, which have been successfully treated, are not excluded.)
6. Treatment with the following within the timeframe specified prior to the first dose:
    - Chemotherapy, radiotherapy, immunotherapy or major surgery < 3 weeks
    - Radioimmunotherapy < 8 weeks
    - Other non-myelosuppressive biologic response modifiers < 2 weeks

Objectives

The primary objective of this study was to evaluate Progression-Free Survival (PFS).
The secondary objectives were to evaluate safety and efficacy using safety and tolerability, Objective Response Rate (CR + CRu +PR) and Overall Survival (OS).
The exploratory analyses are including but not limited to: Time to Response, Duration of Response, Time to Treatment Failure (TTF), Time to Tumour Progression (TTP), Population pharmacokinetic, pharmacodynamic, and pharmacogenomic analysis.

Progression-Free Survival
Progression-free survival is the interval from the date of randomization until the earlier date of progression of disease (PD) or death from any cause. Only documented PD is considered in the independent assessment, (symptomatic deterioration is also considered for investigator's assessment) or death from any cause will be considered as an event.

Patients who withdrew from the study without PD or death are censored at last tumor assessment. If a subject died more than 4 months after last tumor assessment without PD, then the PD is censored at the last valid tumor assessment date. A tumor assessment was considered to be valid for the primary analysis if it could be evaluated by independent review.
In addition to the primary PFS analysis using the independent radiologist and oncologist data, 3 sensitivity analyses were conducted to evaluate the robustness of the results of the primary analysis.

Objective Response Rate
The criteria for objective response are derived from the International Workshop to standardize Response Criteria in NHL. The study protocol provides an attachment tabulating the deviations from the original criteria and the rationale for these deviations. Main modifications are as follows:

- For response assessment a neck CT is required, physical examination is required to record sites that are not accurately monitored by CT and bone lesions are addressed as non-index lesions.
- For CR one BMP is sufficient
- PD requires that lesions (new or known) have a size of at least 2 cm with the rationale that the original criteria are too restrictive for small lesions.

Overall Survival
The overall survival or survival time is defined as the time from randomization to death due to any cause.

Statistics and conduct

The first null hypothesis for primary efficacy comparison will be that progression-free survival between the temsirolimus 75 mg and investigator's choice therapy groups is the same. The first alternative hypothesis will be that progression-free survival is not the same.
The second null hypothesis for primary efficacy comparison will be that progression-free survival between temsirolimus 25 mg and investigator's choice therapy groups is the same. The second alternative hypothesis will be that progression-free survival is not the same.
To detect a hazard ratio of 2.07 total 105 events (progression or death) are required to be observed. With a sample size of 150 evaluable patients, the estimated total study duration is 15.5 months (accrual time will be approximately 12 months and follow-up will continue for all patients until approximately 3.5 months after the last subject is randomized).
The primary analyses were to be performed after 105 PFS events are observed on basis of the intent-to-treat (ITT) population. The primary analysis are to be carried out by using a 2-sided log-rank test at the 2.5% significance level to compare progression-free survival between 2 treatment groups for each hypothesis (overall 5% significance level for 2 comparisons; Bonferroni adjustment).
Progression-free survival rates are estimated using the Kaplan-Meier method. Hazard ratio and the corresponding 95% confidence intervals between 2 treatment arms are calculated using the Cox proportional hazard model, with a single dichotomous covariate for treatment.

The original protocol, dated 28 Oct 2004, was amended 4 times before 29 Aug 2007, the database cutoff date for this report. The protocol including amendment 4 is submitted.
After the data cut-off for this study, the protocol was further amended (Amendment 5) to allow patients in the temsirolimus 175/25-mg or investigator's choice groups to cross over into the temsirolimus 175/75-mg treatment group. Efficacy assessments are no longer required for the patients remaining in the study.

Results

A total of 162 patients were randomly assigned to the 3 treatment groups in the study (ITT population) with 54 patients in each of the 3 groups. The first patient was enrolled in June 2005 and field data cut-off was 19 July 2007, the study is ongoing. Patients were enrolled at 108 investigational sites in 15 countries throughout the world by region. The majority are from Western Europe, Canada, and Australia (region 2) with 69.8% of the study population.

Of 162 patients in the ITT population, 161 entered the treatment phase of the study and received at least 1 dose of study medication (1 patient in the investigator's choice group did not receive study treatment). These 161 patients were evaluable for safety and constituted the safety population.
As of 29 Aug 2007 (the database cutoff date for this report), 25 patients (15%) remained on treatment: 12 (22%) in the temsirolimus 175/75-mg group, 11 (20%) in the temsirolimus 175/25-mg group, and 2 (4%) in the investigator's choice group.
The main reason for discontinuation in all groups is disease progression, followed by discontinuation due to AEs. Particularly, in the temsirolimus 175/75 group discontinuation due to AEs is highest and discontinuation due to disease progression is the lowest. Discontinuations due to investigators request, other or subject request are highest in the investigators choice arm.

Treatment in the Investigators Choice group
Patients in the investigator's choice group received 1 of the following treatments:

- Gemcitabine 22 patients
- fludarabine 14 patients: 12 IV and 2 oral,
- chlorambucil oral 3 patients
- cladribine IV 3 patients
- etoposide IV 3 patients
- cyclophosphamide oral 2 patients
- thalidomide oral 2 patients
- vinblastine IV 2 patients
- Alemtuzumab IV 1 subject
- lenalidomide oral 1 subject

Baseline data
Across all treatment groups, patients were predominantly male (81.5%) and white (89.5%), with a median age of 67 years (range 39 to 88 years), and most (78.4%) had stage 4 disease at diagnosis. Most patients (74.7%) had typical histology grade and 8% of the patients had blastoid histology. The most common cell structures were diffuse (40.1%) and nodular (23.5%). Most patients (80.7%) had more than 6 sites of disease and most (71.2%) had 1 or 2 extranodal sites; almost half had bone marrow involvement. The most common sites of disease were the lymph nodes (93.2%), lungs (27.2%), bone (22.2%), intestinal tract (19.1%), and skin (11.1%). All patients had received prior chemo-, immuno-, radioimmuno-, hormonal, or biologic therapy, and 32.1% and 35.2% had received prior HSCT and radiotherapy, respectively. The patients had received a median of 3.5 prior regimens of therapy.

Efficacy outcome

Progression-free survival
Progression-free survival (PFS) was measured from the date of randomization to the earlier date of either disease progression or death (from any cause within 4 months of the last valid tumor assessment), and censored at the last tumor evaluation date or 19 Jul 2007 (the field data cut-off date), whichever was earlier.

Independent assessment
The primary PFS analysis was based on the independent assessment of progression.
As of 19 Jul 2007, PFS events were reported for 105 patients in the ITT population based on the independent assessment. Censoring dates were used for the other patients.
The median PFS was

- 4.8 months in the temsirolimus 175/75-mg group,
- 3.4 months in the temsirolimus 175/25-mg group, and
- 1.9 months in the investigator's choice group.

Based on the independent assessment and the definition above, the difference in PFS between temsirolimus 175/75 and investigator's choice was statistically significant with a HR (97.5%CI) of 0.44 (0.25, 0.78); and log-rank p-value 0.0009.

The difference between temsirolimus 175/25 and investigator's choice was not statistically significant with HR (97.5%CI) of 0.65 (0.39; 1.10) and log-rank p-value 0.0618.

Investigator assessment

The analysis on PFS by Investigator assessment was performed as a sensitivity analysis. As of 19 Jul 2007, PFS events were reported for 118 patients based on the investigator assessment. Censoring dates were used for the other patients.

The median PFS was

- 4.8 months in the temsirolimus 175/75-mg group,
- 3.7 months in the temsirolimus 175/25-mg group, and
- 1.8 months in the investigator's choice group.

Based on the investigator assessment of PFS, comparison of both temsirolimus groups with investigator's choice were statistically significant.

The Hazard Ratios are 0.39 and 0.41, respectively; and the log-rank p-values <0.0001.

The results are displayed in the following table and Kaplan-Meier plot.

Table 9-3: Progression-Free Survival
ITT Population

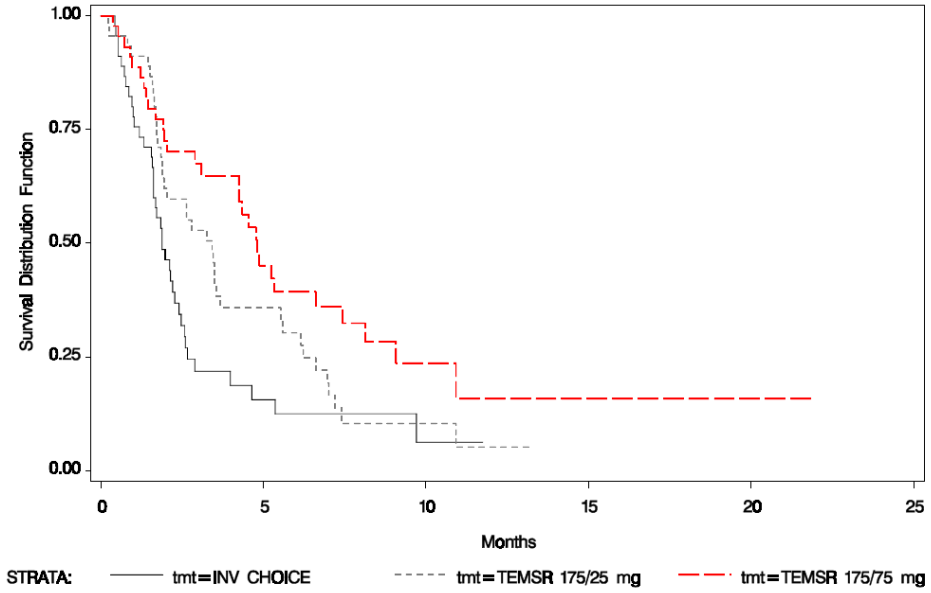
	TEMSR 175/75 mg (N=54)	TEMSR 175/25 mg (N=54)	INV CHOICE (N=54)
Independent Assessment [a]			
No. subjects with PD or who died (n, %)	29(53.8)	38(70.4)	38(70.4)
No. censored subjects (n, %)	25(46.2)	16(29.6)	16(29.6)
Median PFS in months (97.5% CI)	4.8 (3.1, 8.1)	3.4 (1.9, 5.5)	1.9 (1.6, 2.5)
% Change in median PFS from INV CHOICE	153%	79%	
Hazard ratio [b] (97.5% CI)	0.44 (0.25, 0.78)	0.65 (0.39, 1.10)	
p-Value [c]	0.0009	0.0618	
Investigator Assessment [d]			
No. subjects with PD or who died (n, %)	35(64.8)	38(70.4)	45(83.4)
No. censored subjects (n, %)	19(35.2)	16(29.6)	9(16.6)
Median PFS in months (95% CI)	4.8 (2.9, 7.0)	3.7 (3.4, 6.2)	1.8 (1.6, 2.0)
% Change in median PFS from INV CHOICE	167%	106%	
Hazard ratio [b] (95% CI)	0.39 (0.25, 0.63)	0.41 (0.26, 0.65)	
p-Value [c]	<.0001	<.0001	

a. Disease assessment is based on radiographic review by independent radiologists and review of clinical data by independent oncologists.
b. Compared with INV CHOICE based on Cox proportional hazard model.
c. Compared with INV CHOICE based on log-rank test.
d. Disease assessment is based on review of radiographic and clinical data by the investigator.

Abbreviations: CI = confidence interval; ITT = intent-to-treat; No. = number; PD= progressive disease; PFS= progression-free survival.

Source: /CLINICAL R&D/CLINICAL PROGRAMMING SAS REPORTS/3066K1 CCI-779/305/UNBLIND 29AUG07/HTML/3066-305 pfs_itt.htm - 24SEP07 16:03

Figure 9-1: Progression-Free Survival in the ITT Population (Independent Assessment)



Abbreviation: ITT = intent-to-treat.
/CLINICAL R&D/CLINICAL PROGRAMMING SAS REPORTS/3066K1 CCI-779/305/UNBLIND 29AUG07/CGM/KM305_2.doc 15:14

The reasons for censoring are presented in the following table: The number of censored patients is highest in the temsirolimus 175/75 group. For the primary analysis more patients were censored in the temsirolimus 175/75 group compared to investigator's choice. Main reasons were “on treatment” and “late death”.

Table 9-2: Reasons for Censoring in Progression-Free Survival Analyses ITT Population

Reason	TEMSR 175/75 mg (N=54)	TEMSR 175/25 mg (N=54)	INV CHOICE (N=54)	Total (N=162)
Independent Assessment [a]				
Any Reason	25 (46.3)	16 (29.6)	16 (29.6)	57 (35.2)
Alive and in follow-up	5 (9.3)	3 (5.6)	9 (16.7)	17 (10.5)
Late death [b]	8 (14.8)	3 (5.6)	3 (5.6)	14 (8.6)
Lost to follow-up[c]	0	1 (1.9)	2 (3.7)	3 (1.9)
On treatment	12 (22.2)	9 (16.7)	2 (3.7)	23 (14.2)
Investigator Assessment [d]				
Any Reason	19 (35.2)	16 (29.6)	9 (16.7)	44 (27.2)
Alive and in follow-up	3 (5.6)	4 (7.4)	5 (9.3)	12 (7.4)
Late death [b]	3 (5.6)	0	1 (1.9)	4 (2.5)
Lost to follow-up[c]	0	1 (1.9)	1 (1.9)	2 (1.2)
On treatment	13 (24.1)	11 (20.4)	2 (3.7)	26 (16.0)

a. Disease assessment is based on radiographic review by independent radiologists and review of clinical data by independent oncologists.
b. A late death is defined to be any death that occurred more than 4 months after the last tumor assessment without PD.
c. Lost to follow up includes subjects who withdrew consent.
d. Disease assessment is based on review of radiographic and clinical data by the investigator.

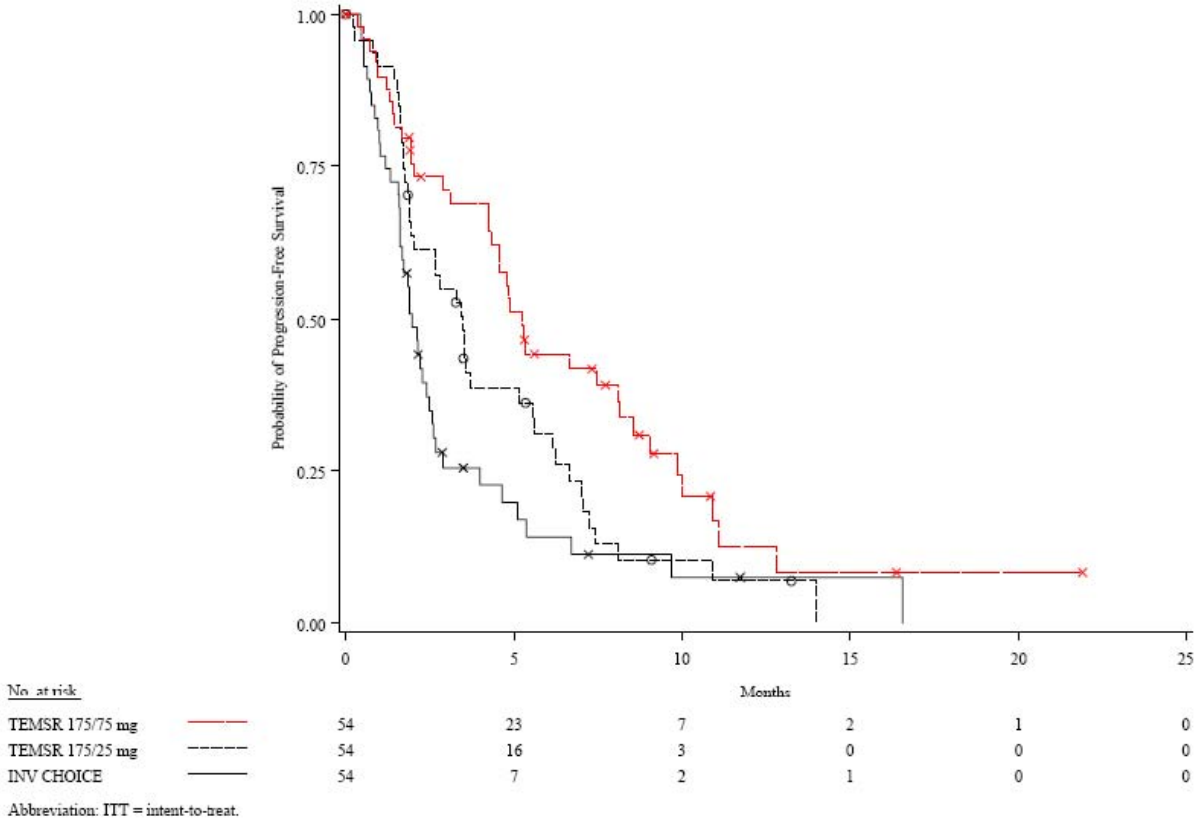
Abbreviations: ITT = intent-to-treat; PD = progressive disease.
Source: /CLINICAL R&D/CLINICAL PROGRAMMING SAS REPORTS/3066K1 CCI-779/305/UNBLIND 29AUG07/HTML/3066-305 pfs_cnsr_itt.htm - 25SEP07 14:49

Table 2-1: Progression-Free Survival (ITT Population, All Deaths)

	TEMSR 175/75 mg (N=54)	TEMSR 175/25 mg (N=54)	INV CHOICE (N=54)
Independent Assessment[a]			
No. patients with PD or who died (n, %)	37(68.6)	41(76.0)	41(76.0)
No. censored patients (n, %)	17(31.4)	13(24.0)	13(24.0)
Median PFS in month (95% CI) Hazard ratio[b] (95% CI)	5.2 (4.3, 8.1) 0.46 (0.29, 0.72)	3.5 (1.9, 5.5) 0.68 (0.44, 1.06)	2.0 (1.6, 2.5)
P-value[c]	0.0007	0.0881	
Investigator Assessment[d]			
No. patients with PD or who died (n, %)	38(70.4)	38(70.4)	46(85.2)
No. censored patients (n, %)	16(29.6)	16(29.6)	8(14.8)
Median PFS in month (95% CI) Hazard ratio b (95% CI)	4.9 (3.1, 7.0) 0.44 (0.28, 0.68)	3.7 (3.4, 6.2) 0.48 (0.31, 0.75)	1.8 (1.6, 2.1)
P-value[c]	0.0002	0.0009	

a. Disease assessment is based on radiographic review by independent radiologists and review of clinical data by independent oncologists.
b. Compared with INV CHOICE based on Cox proportional hazard model.
c. Compared with INV CHOICE based on log-rank test.
d. Disease assessment is based on review of radiographic and clinical data by the investigator. Abbreviations: CI = confidence interval; ITT = intent-to-treat; No. = number; PD = progressive disease; PFS = progression-free survival.

Figure 2-1: Progression-Free Survival in the ITT Population (Independent Assessment) Treating All Deaths as Events



The results presented above including all deaths in the primary analysis model on PFS are in line with the results as reported primarily. The difference in PFS is 3.2 months when all deaths are included and 2.9 months as reported for the primary analysis.

To address the most conservative estimate an analysis that combines independent and investigator assessment was performed. The difference in PFS in this analysis was 2.5 months between temsirolimus 175/75 mg and investigator's choice. A number of sensitivity analyses were undertaken, (incl. analysis on TTF with treatment change as an event, excluding blastoid histology) and the HR and CIs are found in a similar range for all these sensitivity analyses indicating a robust result so far.

Overall survival

Overall survival (OS) was measured from the date of randomization to the date of death. As of the field data cut-off date of 19 Jul 2007, 91 patients in the ITT population died as documented in the clinical database:

- 29 patients in the temsirolimus 175/75-mg group,
- 31 patients in the temsirolimus 175/25-mg group, and
- 31 patients in the investigator's choice group.

Based on these events the median OS was

- 10.9 months in the temsirolimus 175/75-mg group,
- 8.5 months in the temsirolimus 175/25-mg group, and
- 5.8 months in the investigator's choice group.

Both comparisons showed no significance with HR of 0.62 (95 % CI 0.37, 1.05) and 0.80 (95 % CI 0.48, 1.33) respectively; and log-rank p-values 0.0714 and 0.3876, respectively.

The results are displayed in the following table and in the Kaplan-Meier plot.

Table 9-4: Overall Survival ITT Population

	TEMSR 175/75 mg (N=54)	TEMSR 175/25 mg (N=54)	INV CHOICE (N=54)
No.deaths (n, %)	29(53.8)	31(57.4)	31(57.4)
Median OS in months (95% CI)	10.9 (8.1, 14.1)	8.5 (5.8, 14.0)	5.8 (4.8, 12.4)
% Change in median OS from INV CHOICE	88%	47%	
Hazard ratio [a] (95% CI)	0.62 (0.37, 1.05)	0.80 (0.48, 1.33)	
p-Value [b]	0.0714	0.3876	

a. Compared with INV CHOICE based on Cox proportional hazard model.
b. Compared with INV CHOICE based on log-rank test.
Abbreviations: CI = confidence interval; ITT = intent-to-treat; No. = number; OS= overall survival
Source: /CLINICAL R&D/CLINICAL PROGRAMMING SAS REPORTS/3066K1 CCI-779/305/UNBLIND 29AUG07/HTML/3066-305 surv_itt.htm - 14SEP07 14:52

Figure Overall survival (pivotal study 3066K1-305-WW)

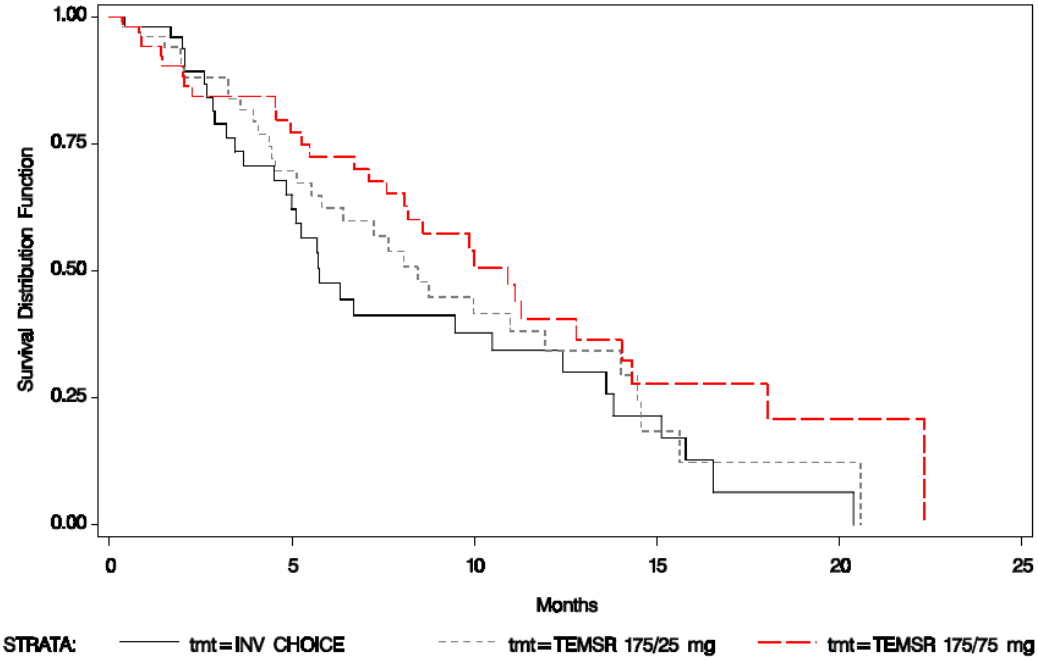


Table 3-3: Overall Survival Including Site-Reported Data (01 Feb 2008)
ITT Population

	TEMSR 175/75 mg (N=57)	TEMSR 175/25 mg (N=56)	INV CHOICE (N=56)
No.deaths (n, %)	34(59.6)	37(66.0)	37(66.0)
Median OS in month (95% CI)	12.8 (8.6, 22.3)	11.0 (7.7, 15.6)	10.3 (5.8, 15.8)
% Change in Median OS from INV CHOICE	24%	7%	
Hazard ratio [a] (95% CI)	0.78 (0.49, 1.24)	1.00 (0.63, 1.58)	
p-Value [b]	0.2970	0.9950	

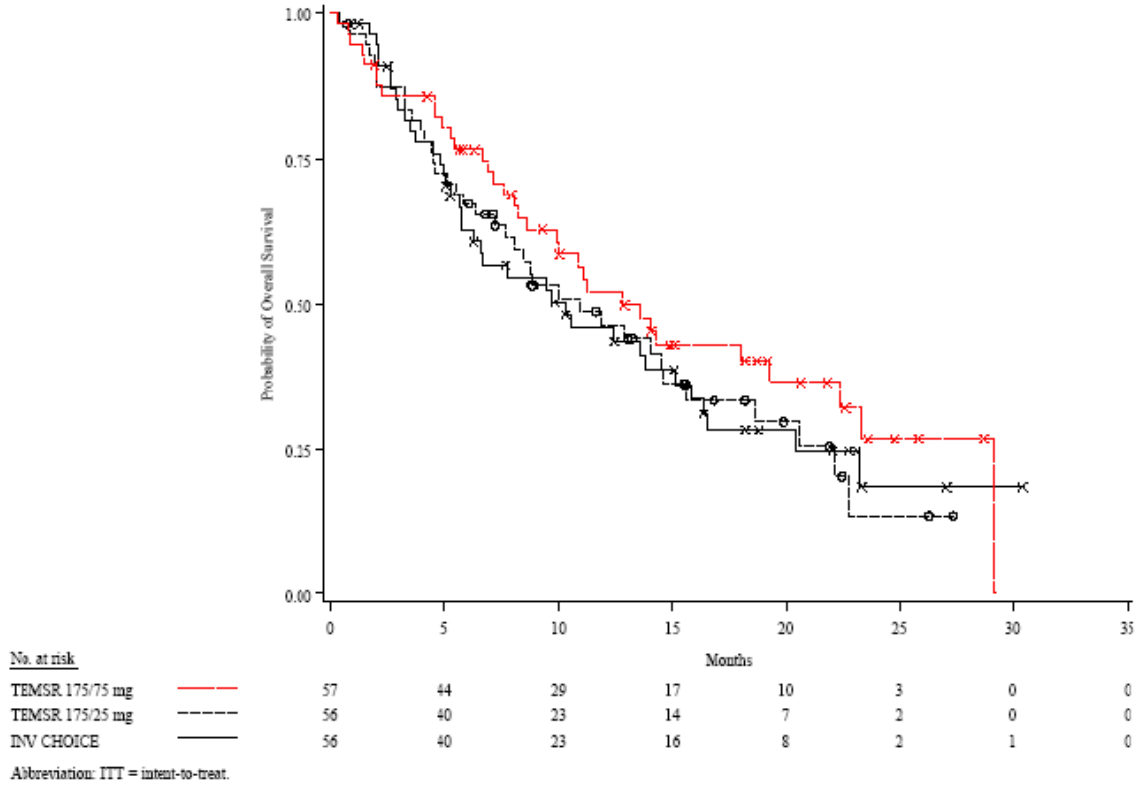
Abbreviations: CI = confidence interval; OS = overall survival

a. Compared with INV CHOICE based on Cox proportional hazard model.

b. Compared with INV CHOICE based on log-rank test.

source: /CLINICAL R&D/CLINICAL PROGRAMMING SAS REPORTS/3066K1 CCI-779/305/CDRs SURVIVAL SWEEP/3066-305 SURV_305_SWP - 20AUG08 08:49

Figure 3-3: Overall Survival in the ITT Population Including Site-Reported Data (01 Feb 2008)



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In none of the three different analyses on the updated OS data from study 3066K1-305-WW, was there any significant difference between either of the temsirolimus arms and the investigator's choice arm: The OS, including site-reported data until Feb 1 2008 (ITT population), showed estimates for median OS 12.8 months (95% CI, 8.6 to 22.3) in the temsirolimus 175/75-mg group, 11.0 months (95% CI, 7.7 to 15.6) in the temsirolimus 175/25-mg group, and 10.3 months (95% CI, 5.8 to 15.8) in the investigator's choice group. In the early phase the curves interchange and at approx.12 months they approach each other. For the longer follow-up the patient numbers are very small.

Therefore, only the primary endpoint PFS has been found to be approx. 3 months longer in the temsirolimus 175/75-mg group than in the investigator choice treatment group with a statistically significant effect and no significant difference in overall survival has been demonstrated. The trend in favour of temsirolimus that was seen in the updated analysis is far less impressive than in the first one.

Objective response rate

Objective response rate (ORR) was the percentage of patients who had a confirmed complete or partial response (CR, CRu, or PR) as their best response to treatment as of the database date (29 Aug 2007). Patients underwent a complete disease assessment and CT scans of the neck, chest, abdomen, and pelvis approximately every 8 weeks during the first year, every 12 weeks during the second year, and every 6 months in years 3 to 5 until disease progression.
There were 2 sets of tumour assessments (investigator and independent) performed in the study.

Table 9-5: Best Overall Response
ITT Population

Reason	TEMSR 175/75 mg (N=54)	TEMSR 175/25 mg (N=54)	INV CHOICE (N=54)
Independent Assessment [a]			
Assessment not available [b]	14 (25.9)	11 (20.4)	14 (25.9)
Complete response (CR)	1 (1.9)	0	1 (1.9)
Partial response (PR)	11 (20.4)	3 (5.6)	0
Stable disease (SD) [c]	16 (29.6)	17 (31.5)	11 (20.4)
Progressive disease (PD)	12 (22.2)	23 (42.6)	28 (51.9)
Investigator Assessment [d]			
Assessment not available [e]	17 (31.5)	15 (27.8)	7 (13.0)
Complete response (CR)	2 (3.7)	1 (1.9)	0
Partial response (PR)	5 (9.3)	7 (13.0)	1 (1.9)
Stable disease (SD) [c]	19 (35.2)	18 (33.3)	16 (29.6)
Progressive disease (PD)	11 (20.4)	13 (24.1)	30 (55.6)

Best overall response was determined at each time point for the independent assessment and only at the end-of-treatment visit for the investigator assessment.

a. Disease assessment is based on radiographic review by independent radiologists and review of clinical data by independent oncologists.
b. Independent assessments were not available in cases where assessment were not of the quality required for reading by the independent reviewer, were missing, or were not yet read by the independent reviewer.
c. Must have met the stable disease criteria at least once after randomization at a minimum of 8 weeks (2-week window).
d. Disease assessment is based on review of radiographic and clinical data by the investigator.
e. Investigator assessments of best overall response were not available for subjects who came off study without having an end-of-treatment visit or who had not had an end-of-treatment visit before the data cutoff date.

Abbreviations: CR= complete response; CRu=complete response, unconfirmed; ITT = intent-to-treat; PD=progressive disease; PR=partial response; SD=stable disease.

Source: /CLINICAL R&D/CLINICAL PROGRAMMING SAS REPORTS/3066K1 CCI-779/305/UNBLIND 29AUG07/HTML/3066-305 - BESTRESP_ITT - 16OCT07 09:10

Thus, both temsirolimus groups had improvements in ORR compared with the investigator's choice group. Per independent assessment, the improvement in ORR compared with investigator's choice was statistically significant for the temsirolimus 175/75-mg group (p-value 0.0019), but not for the temsirolimus 175/25-mg group (p-value 0.6179); per investigator assessment, the improvement in ORR compared with investigator's choice was not statistically significant for the temsirolimus 175/75-mg group (p-value 0.0602), but was for the temsirolimus 175/25-mg group (p-value 0.0314).

Time to response

Analyses of the exploratory endpoints of time to response, duration of response, and TTP were based on both the investigator and the independent assessments of tumor progression; TTF was based on the investigator assessment. A summary of the results for these endpoints is provided in the Table below. There were no significant differences in the time to response or duration of response between either of the temsirolimus groups and the investigator's choice group using either the independent or the investigator assessments.

Table: Response rate, time to response and duration of response (pivotal study 3066K1-305-WW)

	TEMSR 175/75 mg	TEMSR 175/25 mg	INV CHOICE
Time to Response			
(median in months; subjects with response)			
Independent Assessment [a]	3.6 (12 subjects)	3.5 (3 subjects)	4.0 (1 subject)
Investigator Assessment [b]	1.8 (7 subjects)	1.7 (8 subjects)	1.8 (1 subject)
Duration of Response			
(median in months; subjects with response)			
Independent Assessment [a]	7.1 (12 subjects)	3.6 (3 subjects)	N/A[c] (1 subject)
Investigator Assessment [b]	5.8 (7 subjects)	3.7 (8 subjects)	N/A[c] (1 subject)
Time to Tumor Progression			
(median in months; ITT population; 54 subjects per group)			
Independent Assessment [a]	5.2*	3.5	1.9
Investigator Assessment [b]	4.9*	3.7*	1.8
Time to Treatment Failure			
(median in months; ITT population; 54 subjects per group)			
Investigator Assessment [b]	3.1*	3.4*	1.7

* Indicates statistically significant difference from investigator's choice treatment, based on log-rank test.

a. Disease assessment is based on radiographic review by independent radiologists and review of clinical data by independent oncologists.

b. Disease assessment is based on review of radiographic and clinical data by the investigator.

c. Duration of response for the 1 subject in the investigator's choice group was at least 5.1 months per independent assessment and at least 7.8 months per investigator assessment (based on censoring at the last tumor assessment because the subject did not have disease recurrence or progression before the database cutoff date of 29 Aug 2007).

Abbreviations: ITT = intent-to-treat; N/A = not applicable.

Ancillary analyses

In addition to the analysis of PFS based on the investigator assessment, 2 more sensitivity analyses of PFS were conducted.
The results of sensitivity analysis 3 of PFS using the first PFS event date per independent or investigator assessment plus all death dates included 20 more PFS events than the primary analysis:

- 8 in the temsirolimus 175/75-mg group,
- 3 in the temsirolimus 175/25-mg group, and
- 9 in the investigator's choice group.

Hazard ratios were 0.40 (95% CI, 0.26-0.63) comparing the temsirolimus 175/75-mg and investigator's choice groups and 0.50 (95% CI, 0.33-0.77) comparing the temsirolimus 175/25-mg and investigator's choice groups. The difference in PFS curves between both temsirolimus groups and the investigator's choice group was statistically significant (log-rank p-values <0.0001 and 0.0012). The difference between the temsirolimus 175/25-mg group and the investigator's choice group was not statistically significant in the primary efficacy analysis.

Clinical studies in special populations

Subpopulation analyses of PFS and OS by baseline demographic and disease characteristics were performed. The results of analyses of PFS and OS by age, sex, race, region, and baseline characteristics were consistent with the results for the ITT population. There was no evidence of differences in efficacy based on any of these factors, so there are no recommendations for specific dose adjustments based on age, sex, or other characteristics.

The current database in MCL with 108 patients exposed to temsirolimus is probably too small to give any reliable estimate for a particular subgroup.

Discussion on Clinical Efficacy

The pivotal study undertaken in mantle cell lymphoma is a randomised Phase 3, open-label, multicentre, 3-arm study comparing temsirolimus monotherapy in 2 different dosage regimens with

investigator's choice of single agent. For the included patient population with relapsed mantle cell lymphoma pre-treated with 2-7 regimens there is no evidence based comparator. Therefore, the comparator “investigator's choice of single agent” is considered adequate.

Patients included in the pivotal trial 3066K1-305-WW were representative for the target indication, all pretreated with a median number of regimens of 3.5 including rituximab. Taking into account the overall expectation of survival for patients with MCL (median overall survival of 3-4 years), median interval between diagnosis and randomisation was quite long with 45 months for all patients. Patient characteristics were in general well balanced between treatment groups.

With the presented analyses the study met its primary endpoint. Based on the independent assessment, median PFS was 4.8 months in the temsirolimus 175/75-mg group and 1.9 months in the investigator’s choice group (HR=0.44,; log-rank value 0.0009). The median PFS of 3.4 months in the lower dose temsirolimus 175/25-mg group was not statistically significantly different compared to the investigator’s choice group (HR=0.65; log-rank p-value 0.0618).

The difference in PFS is 3.2 months when all deaths are included in the primary model while 2.9 months were reported for the primary analysis. To address the most conservative estimate an analysis that combines independent and investigator assessment was performed. The difference in PFS in this analysis was 2.5 months between temsirolimus 175/75 mg and investigator's choice.
A number of sensitivity analyses were undertaken, including analysis of TTF with treatment change as an event, excluding blastoid histology. The HR and CIs are found in a similar range for all these sensitivity analyses indicating a robust result so far.

However, these effects did not translate into a benefit in terms of prolongation of overall survival. The median OS was not statistically significant between treatment arms: 10.9 months in the temsirolimus 175/75-mg group, 8.5 months in the temsirolimus 175/25-mg group, and 5.8 months in the investigator's choice group (log-rank p-values 0.0714 and 0.3876, respectively).

Thus, only the primary endpoint PFS has been found to be approximately 3 months longer in the temsirolimus 175/75-mg group than in the investigator choice treatment group and statistically significant, and no significant difference in overall survival has been demonstrated. Further, the trend in favour of temsirolimus that was seen in the updated analysis is far less impressive than in the first presentation: The overall survival, including site-reported data until Feb 1 2008 (ITT population), showed estimates for median OS of 12.8 months (95% CI, 8.6 to 22.3) in the temsirolimus 175/75-mg group, 11.0 months (95% CI, 7.7 to 15.6) in the temsirolimus 175/25-mg group, and 10.3 months (95% CI, 5.8 to 15.8) in the investigator's choice group. In the early phase the curves interchange and at approximately 12 months they approach each other.

It is agreed with the MAH that in lymphoma cytotoxicity is important for disease control and temsirolimus acts mainly as a cytotoxic agent with > 20 % ORR (per independent review). The observed results for ORR, and PFS support a dose dependent efficacy.

However, the rationale for the selection of the ‘175mg/75mg’ and ‘175mg/25mg’ i.v. doses of temsirolimus is not yet considered adequately justified. The 175 mg dose is much higher than the dose licensed for renal cell carcinoma (RCC, 25 mg i.v. weekly). The information submitted for RCC in the wide dose range investigated, showed dose-related increases in exposure, as measured by temsirolimus Cmax, AUC and AUCsum in whole blood, increased with dose, but significantly was not entirely proportional ($p < 0.001$) due to saturable binding of temsirolimus to FKBP12 in blood cells and peripheral compartments. The MTD was determined to be 220 mg/m^2 (2 out of 6 patients (33%) who had drug-related unacceptable toxicity during the first 21 days of treatment: Grade 3 stomatitis and asthenia).

For the Phase 3 study in renal cell carcinoma, 25 mg dose of temsirolimus as single agent was chosen as the lowest dose associated with activity, on the basis that patients randomised to receive 25, 75 or 250 mg of temsirolimus IV exhibited comparable clinical activity. While the incidence of TEAE, NCI

Grades 3 or 4 TEAEs or SAEs was not significantly different among the different doses, there was a trend of a reduction in the number of doses with the increase in dose.

For mantle cell lymphoma, the MAH refers to the phase II study published by Witzig and colleagues (JCO 2005; 23: 5347) in which 35 patients with previously treated MCL were treated with temsirolimus 250 mg weekly as a single agent. The overall response rate was 38%; dose reductions were necessary in all but four patients with thrombocytopenia being the most common side effect. The study was amended to allow multiple dose reductions as low as 50 mg weekly. The authors concluded that 'further studies with additional sets of serial MCL samples would be needed or circulating mononuclear cells to better determine whether temsirolimus induced changes in S6 phosphorylation predict response to therapy'. In the currently submitted study, the investigators state that pharmacodynamic studies are incorporated.

The authors of this first study (Witzig et al) reported that they went on investigating the 25-mg weekly i.v. dose level in a new cohort (N=29) of patients with relapsed/refractory MCL (data published by Ansell et al; JCO 2006: 7532 (abstract)). The ORR was 41% (11/27) (higher than the goal to achieve an ORR of at least 20%), with 1 CR and 10 PRs. Evaluation of TTP showed a median of 5.5 months (95% CI: 3.3–7.7) and the duration of response for the 11 responders was 6.2 months (95% CI: 3.6 to not yet reached). According to the authors, the results compare favourably with the 6.5 months and 6.9 months, respectively, found in the previous trial that used 250 mg.

Of special interest is the recently published report by the investigator initiated study N0186, concerning treatment of a small number of patients (29) with relapsed or refractory MCL with a "flat" dose of 25 mg temsirolimus (Ansell et al., Cancer 113(2008)508-514). This single arm study seems to have been carried out under similar conditions as study 3066K1-305-WW. In this report, efficacy was investigated in 27 patients. The median time to progression (TTP) was 6 months (95% CI 3 – 11 months). This result comes close to that found under similar circumstances for the PFS in study 3066K1-305-WW both in the 175/75mg arm: 4.9 months (95% CI 3.1-7.0, ITT population, "all deaths") and is longer than in the 175/25-mg arm (3.7, 95% C I 3.4 – 6.2) both under assessment by the investigator. In the recently published data, doses of 15 mg and 10 mg were also given if the dose had to be reduced due to adverse effects.

The MAH has stated that the 175 mg step in the dosage regime chosen was based on data from Study N0186 in which a mean dose of 175 mg was tolerated weekly for 4 weeks and the 75 mg or 25 mg were chosen since they had been shown to be effective in other tumour types, and there were also indications that 25 mg was also active in MCL. The MAH stated that the 75 mg dose is supported by a simulation of whole blood concentrations of sirolimus. In the pivotal study 3066K1-305-WW a significant difference in PFS was found between the 175/75-mg group and the investigator's choice group both in the case of investigator and independent assessment of PFS. For the 175/25-mg group a significant difference with the investigator's choice group was only seen in the case of assessment of PFS by the investigator. These observations are not being disputed by the CHMP but they do not provide a rationale for choosing for example the 75 mg dose, or the 175 mg starting dose.

Thus, the CHMP considers that further investigations are needed to address the question of posology particularly with reference to whether the initial 3 weeks of exposure to 175 mg weekly contribute to the efficacy outcome.

Upon request by the CHMP, the applicant has committed to conduct a randomised clinical study in patients with MCL to explore whether similar efficacy can be achieved with a less toxic dose regimen. The agreed study is a randomized 2-arm trial which will enrol a total of 100 subjects to receive treatment with either temsirolimus at 175/75 mg (i.e., 175 mg IV per week x 3 doses, followed by 75 mg IV per week) or 75 mg IV given weekly. The primary efficacy objective of this study will be to estimate the hazard ratio (HR) comparing progression-free survival (PFS; as assessed by independent radiological review) between the 2 treatment arms using the Cox Proportional Hazard model. Secondary endpoints will include the estimation of objective response rate (ORR) as well as the estimation of safety profiles (including the prevalence of particular adverse events, such as bleeding, infection and mucositis) for each of the 2 treatment arms.

The MAH will provide the results or this study within agreed timeframes for CHMP review.

Until these data become available and based on the limited information that is assessable now, the SPC and Package Leaflet have been updated with a warning to reflect that the toxicity of the 175 mg dose is substantially more pronounced than the dose authorised for RCC. The SPC highlights that the starting dose of 175 mg was associated with a significant incidence of adverse events and required dose reductions/delays in the majority of patients (see discussion on clinical safety below). Further, the SPC informs prescribers of the fact that the contribution of the initial 175 mg doses to the efficacy outcome is currently not known.

Clinical Safety

Exposure

The safety profile of temsirolimus in patients with relapsed and/or refractory MCL is derived exclusively from study 3066K1-305-WW; therefore the data from this study is the focus. Pooling of safety results from this study with those from other studies was not performed because no other studies were conducted in this subject population and the dosing regimen in this study was unique (3 weeks of a high loading dose before weekly administration at a dose similar to that used in other studies). Comparisons are drawn between the safety profile of temsirolimus for patients with MCL and the previously defined safety profile of temsirolimus for patients with advanced RCC.

In study 3066K1-305-WW, 161 of the 162 patients who were randomly assigned received treatment: 54 in the temsirolimus 175/75-mg group, 54 in the temsirolimus 175/25-mg group, and 53 in the investigator's choice group.

Duration of treatment was longer in the temsirolimus groups than in the investigator's choice group. The median duration of treatment was 12.1 weeks (range, 1 to 97 weeks) in the temsirolimus 175/75-mg group, 14.1 weeks (range, 1 to 172 weeks) in the temsirolimus 175/25-mg group, and 4.6 weeks (range, 1 to 35 weeks) in the investigator's choice group.

The patients in the temsirolimus 175/75-mg group had higher exposure to temsirolimus than those in the temsirolimus 175/25-mg group (median dose intensities 78.8 and 42.3 mg per week, respectively), but in both groups most patients received a lower dose than intended (median relative dose intensities 0.75 and 0.88, respectively).

Dose reductions and delays

Approximately half of the subjects had a dose reduction, and two thirds had a dose delay within the first 3 doses of temsirolimus because of adverse events. Only a minority of patients (46 of 108, 43%) received the 3 full doses of 175 mg. Overall, the median dose intensities during the 3 first weeks of treatment were lower than intended (median relative dose intensities 0.80 and 0.63). After the first 3 doses, the median dose intensity was approximately twice as high for the patients in the temsirolimus 175/75-mg group as for those in the temsirolimus 175/25-mg group (51.0 mg per week vs. 23.3 mg per week). The median relative dose intensity after the first 3 doses, was 0.68 in the patients in the temsirolimus 175/75-mg group and 0.93 in patients in the temsirolimus 175/25-mg group.

Adverse events (AEs)

The distribution of TEAEs, grade 3 and 4 TEAEs, SAEs, AEs leading to discontinuation, AEs leading to dose reductions and AEs leading to dose delays and deaths is presented in the following table. The percentage for all groups is substantially higher in both temsirolimus groups compared to investigator's choice. For the most type of AEs the incidence is highest in the temsirolimus 175/75 mg group.

Table 3-1: Brief Summary of Adverse Events: Number (%) of Subjects

Event	TEMSR 175/75 mg n=54	TEMSR 175/25 mg n=54	INV CHOICE n=53
Any TEAE	51 (94.4)	52 (96.3)	48 (90.6)
Grade 3 or 4 TEAEs	48 (88.9)	43 (79.6)	36 (67.9)
SAEs	28 (51.9)	27 (50.0)	13 (24.5)
AEs leading to discontinuation	18 (33.3)	12 (22.2)	6 (11.3)
AEs leading to dose reductions	33 (61.1)	21 (38.9)	6 (11.3)
AEs leading to dose delays	42 (77.8)	37 (68.5)	23 (43.4)
Deaths (ITT population) within 14 days of last dose	4 (7.4)	2 (3.7)	1 (1.9)

Abbreviations: AE=adverse event; INV=investigator's; ITT=intent-to-treat; SAE=serious adverse event;TEAE=treatment-emergent adverse event; TEMSR; temsirolimus.

Source: /CLINICAL R&D/CLINICAL PROGRAMMING SAS REPORTS/3066K1 CCI-779/305/UNBLIND29AUG07/HTML/3066-305 AE4T 14SEP07 10:13, AE4T_34 14SEP07 10:13, AE4_SAE 14SEP07 10:13,AE4_WITH 14 SEP07 10:13, AE4_REDUCE 14SEP07 10:13, AE4_DELAY 14 SEP07 10:13 , DTH4 14SEP0710:31.

Treatment Emergent Adverse Events (TEAEs)

Nearly all patients in study (>90 % in all treatment groups) had at least 1 treatment emergent adverse event (TEAE). In the phase 3 MCL study, the most frequently affected body systems in the temsirolimus 175/75 mg group were the

- haemic and lymphatic system (90.7%),
- body as a whole (88.9%),
- digestive system (83.3%),
- respiratory system (66.7%),
- metabolic and nutritional system (64.8%),
- skin and appendages (64.8%),
- nervous system (50%),
- special senses (38.9%),
- musculoskeletal system (31.5%), and
- cardiovascular system (27.8%) and
- urogenital systems (27.8%).

These are in principle the same body systems affected as in RCC patients. When considering the adverse events of the higher dose temsirolimus compared to the currently authorized dose of 25 mg i.v. weekly, the relatively small database of 108 patients with MCL being exposed to a much higher dose of 175/75 and 175/25 mg should be taken into account.

Many events were observed with a significantly higher incidence in the temsirolimus 175/75-mg group versus the investigator's choice group ($p<0.05$), the most important differences between treatment groups were thrombocytopenia (72.2% vs 52.8%), asthenia (63.0% vs 26.4%), diarrhea (44.4% vs 9.4%), anorexia (37.0% vs 15.1%), mucositis (35.2% vs 0), rash (35.2% vs 9.4%), epistaxis (35.2% vs 5.7%), infection (27.8% vs 9.4%), pain (27.8% vs 3.8%), cough increased (25.9% vs 9.4%), pruritus (25.9% vs 5.7%), stomatitis (20.4% vs 3.8%), arthralgia (20.4% vs 1.9%), hypokalemia (18.5% vs 0), nail disorder, taste perversion, and upper respiratory infection (14.8% vs 1.9% for each), and dry skin and hypercholesteremia (13.0% vs 0 for each).

Comparing the incidence of TEAEs during the first 3 doses of 175 mg with the further lower doses, the TEAEs whose incidence decreased 2-fold after the fourth dose (at least in one temsirolimus group) were erythema (temsirolimus 175/75-mg group), stomatitis and epistaxis (temsirolimus 175/25-mg group). TEAEs whose incidence increased over 2-fold after the fourth dose (at least in one temsirolimus group) as compared with those that occurred within the first 3 doses were anemia, herpes simplex, nail disorder, hypercholesteremia, hyperlipidemia, hypokalemia, peripheral edema, pneumonia, and weight loss (both temsirolimus groups), anxiety, depression, diarrhea, hyperglycemia, infection, lymphopenia, and vomiting (temsirolimus 175/75-mg group), arthralgia, dyspnea, pain, and paresthesia (temsirolimus 175/25-mg group).

Serious Adverse Events (SAEs)

The incidence of drug-related SAEs was greater in the temsirolimus 175/75-mg and temsirolimus 175/25-mg groups than in the investigator's choice group (22.2% and 33.3% vs. 11.3%). The body systems most often affected by treatment-related SAEs were generally similar to those observed for SAEs overall. Drug-related SAEs that occurred in more than 1 patient in both temsirolimus groups were: asthenia (3 patients), fever (7); neutropenic fever (2), diarrhea (3), thrombocytopenia (4), pneumonia and related terms (9), epistaxis (2).

Adverse events of special interest

Adverse events of special interest were hypersensitivity reactions, haematologic, thrombotic, infection-related, gastrointestinal, metabolic, respiratory and renal events.

Haematologic toxicity was higher in patients with MCL treated with temsirolimus than in RCC (with a recommended much lower dose of temsirolimus 25 mg weekly). This seems not only related to the dose of temsirolimus administered, but also to the included target population of mantle cell lymphoma patients with extensively pretreated and many with bone marrow involvement of the lymphoma. Over 80% of subjects with MCL receiving temsirolimus (in either treatment group) had haematologic TEAEs compared with 39.4% of subjects with RCC receiving 25 mg temsirolimus. Most events of thrombocytopenia were treatment related and grade 3 or 4 in severity, leading to dose delay and dose reduction in a significant number of patients.

The rates of bleeding events and thrombocytopenia grade 3 and 4 is higher with the 175 mg dose compared to 75 mg (25/54 patients) and 25 mg (23/54 patients) and to investigator's choice, which consisted mostly of chemotherapy regimens.

Despite prophylaxis with diphenhydramine or a similar antihistamine, rash was reported in 24.1% of patients in the temsirolimus 175/75-mg group and 16.7% in the temsirolimus 175/25-mg group.

More patients developed increased creatinine in both temsirolimus groups (11.1% and 14.8% respectively for the 175/75 mg and 175/25 mg dose group) while this event was not reported for the investigator's choice group.

Infection-related TEAEs were reported in 50.0% and 55.6% of the subjects in the temsirolimus 175/75-mg and temsirolimus 175/25-mg groups, respectively. The incidence was higher than in the investigator's choice group and infections contribute substantially to the SAEs. The adverse events bronchitis (9.3% and 5.6% for the two temsirolimus arms and 3.8% for the investigator's choice arm) and pneumonia (13% and 28.5% for the temsirolimus arms versus 9.4% for the investigator's choice arms) were considered to be treatment related. Approximately half of the pneumonia and bronchitis events were grade 3 or 4 in severity.

An accumulation of infections in the first 3 weeks is apparent when the number of infections is related to the time on treatment: infections are reported in 27 patients in the first 3 weeks with the 175 mg dose and infections are reported in 41 patients during the further study. Considering a treatment duration of approx. 20 weeks (mean) or approx. 13 weeks (median) in the temsirolimus groups, this suggests that the incidence (per week) of infections is at least twice as high during the time on the 175 mg dose.
The incidences of infections and of grade 3 and 4 infections are apparently higher than in the investigator's choice group.

The incidence of mucositis was also clearly much higher in both temsirolimus groups, with a higher incidence in the 175/75 mg group than the 175/25 mg group (mucositis 35% versus 17%), while this adverse event was hardly reported in the investigators'choice group (0% mucositis and 3.8% stomatis). Hyperlipemia was reported in 9.3% of the 175/75 mg dose group and 20.4% in the 175/25 mg dose group versus 0% in the investigator's choice group. Hypokalemia occurred in 18.5% and 16.7 % of the temsirolimus treated patients (175/75 mg and 175/25 mg dose group respectively) and was

not reported in the investigator's choice group. Skin-related TEAEs were reported for a considerable number of patients, i.e. 46.3% and 31.5% of the subjects in the temsirolimus 175/75-mg and temsirolimus 175/25-mg groups, respectively, and in only 11.3% of patients in the investigator's choice arm.

Comparison of Safety in treatment groups

Globally the toxicity was more pronounced in the temsirolimus 175/75 mg group compared to investigator's choice.

- The incidences of observed toxicity were less for most system organ classes in the investigators choice group.
- The incidence of grade 3 and 4 TEAEs was higher in the temsirolimus groups compared to investigator's choice (88.9% vs. 67.9%).
- The incidence of SAEs was twice as high in the temsirolimus groups (approx. 50 %) compared to investigator's choice (approx. 25 %)
- Although based on small numbers, the number of deaths in the temsirolimus groups is higher for
    - death due to AE (2 and 3 in the temsirolimus groups vs.. 0 in the investigator's choice group)
    - death due to "other" cause (1 and 3 in the temsirolimus groups vs.. 1 in the investigator's choice group)
    - death within 30 days of first dose (3 and 2 in the temsirolimus groups vs. 1 in the investigator's choice group)
    - death with 14 days of last dose (4 and 2 in the temsirolimus groups vs. 1 in the investigator's choice group)
- For more patients in either temsirolimus group than in the investigator's choice group AEs were the reason to discontinue from treatment, for dose delay and dose reductions.
- From the AEs of special interest it is notable that bleeding events, infection-related events, and mucositis related events occurred with a substantial higher incidence in the temsirolimus groups.

The comparison may be influenced by choice of rather well tolerated single agents and the use of different agents with different toxicity profiles in the investigator's choice arm. Furthermore, the time under treatment with temsirolimus was much longer (median 12.1 and 14.1 weeks) than in the investigator's choice group (median 4.6 weeks).

Comparison of safety profiles between MCL and RCC treatments

When the safety profile in the pivotal study in MCL (temsirolimus 175/75 mg weekly) is compared to the safety profile in the RCC pivotal study where 25 mg temsirolimus was administered weekly it is obvious that

- the same system organ classes are affected,
- however, the toxicity to the hemic and lymphatic system is much more pronounced (TEAE incidence in MCL approx. 90 %, RCC approx. 55 %)
- the incidence in grade 3 and 4 TEAEs is higher in MCL (89% vs. 69 %) with a major difference in thrombocytopenia
- the incidence in SAEs is higher (approx. 50 % vs. approx.40 %)
- the incidences of AEs leading to treatment discontinuation, dose reductions, or dose delays inpatients with MCL receiving temsirolimus 175/75 mg were higher (mainly due to thrombocytopenia, asthenia and dyspnea)
- from the AE of special interest it is notable that the incidence of bleeding events, infection-related events, and mucositis related events were at least two times higher than in the RCC study.

Elderly patients

Based on the results of the pivotal phase 3 study for MCL, elderly patients may be more likely to experience certain adverse reactions, including anxiety, depression, dyspnea, leukopenia, myalgia, taste loss, and upper respiratory infection. Similar experiences were also seen in elderly patients treated for RCC. This issue is considered sufficiently addressed through routine risk minimisation activities such as information in the updated SPC for Torisel. Further, the MAH will provide a summary tabulation of all adverse events in the elderly population as part of future PSURs.

Overdose/ medication errors

In the population treated for MCL three patients had experienced temsirolimus overdose, all within the first 2 doses of temsirolimus and due to errors in the dosing calculation performed at the investigational site. One patient did not experience an adverse event, one patient experienced treatment-related AEs of grade 2 fever and grade 1 nausea and dizziness, the third patient got a grade 3 rectal haemorrhage, rectal bleeding and grade 2 diarrhoea.

Due to the potential for medication errors, the MAH has taken steps to reduce these, by an update of the product information in order to include very specific directions on the reconstitution and administration of temsirolimus as well as clear statements on the volumes of temsirolimus before and after dilution. The text in section 6.6 of the SPC "Special precautions for disposal and other handling" has been updated with the following information:
"Note: For mantle cell lymphoma, multiple vials will be required for each dose over 25 mg. Each vial of TORISEL should be diluted according to the instructions below. The required contents from each vial should be combined in one syringe for injection into 250 ml of 0.9% sodium chloride injection, see section 4.2."

This issue is considered sufficiently addressed through routine risk minimisation activities such as information in the updated SPC for Torisel.

Pharmacovigilance

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

Risk Management Plan (RMP)

The MAH submitted an updated risk management plan, which included a risk minimisation plan.

The RMP has been sufficiently updated with data from 6 completed or ongoing clinical studies dealing with patients treated for relapsed and/or refractory MCL. Safety data for the new indication are discussed in the context of the known safety profile of temsirolimus from the already approved indication renal cell carcinoma. A careful review of the safety data for the proposed new indication has not suggested any change in the overall safety profile of temsirolimus, but obviously in the frequencies of some adverse events.

Summary of the Risk Management Plan for Torisel

Section of RMP Updated	Description of Changes (Version 2.4 of RMP dated 13 July 2009)
Section 2.2.1.3 Epidemiological Study Exposure	Addition of information from second interim report for post-authorisation Drug Utilization Study 3066K1-4413-EU.
Section 2.2.1.4 Post Marketing (Non-study) Exposure	Information on post-marketing exposure updated through 18 May 2009.
Section 2.2.2.3 Patients with Hepatic Impairment	Addition of information from final study report for Study 3066K1-152-US.

Section of RMP Updated	Description of Changes (Version 2.4 of RMP dated 13 July 2009)
Section 2.3.2 Actual Post Authorisation Usage Data	Information on post-authorisation usage updated through 18 May 2009.
Section 2.9.4 Safety Issues Arising from Off-label Use	Information regarding updated through 18 May 2009.
Table 3-1 Safety Concerns and Planned Pharmacovigilance Actions	Additional pharmacovigilance information updated to include planned post-authorisation study in MCL patients (Study 3066K1-4438-WW) for risks of infections (including opportunistic), bleeding and mucositis.
Table 3-2 Action Plan for Specific Safety Concerns	Additional pharmacovigilance information updated to include planned post-authorisation study in MCL patients (Study 3066K1-4438-WW) for risks of infections (including opportunistic), bleeding and mucositis.
Table 3-3 Overview of Study Protocols for the Pharmacovigilance plan	Updated status of studies and addition of planned post-authorisation study in MCL patients (Study 3066K1-4438-WW).
Table 3-4 Updates to EU-RMP	Update to Off-label Use (Drug Utilization Study) Section to include information from second interim analysis for Study 3066K1-4413-EU. Update to Use in Hepatic Impaired Patients Section to include the addition of information from final study report for Study 3066K1-152-US.
Table 3-5 Summary of Outstanding Actions	Updated status of studies and addition of planned post-authorisation study in MCL patients (Study 3066K1-4438-WW).
Table 4-1 Safety Concerns and Planned Actions	Routine risk minimization slightly revised for hepatic impairment to reflect SPC.
Table 6-1 Summary of the EU Risk Management Plan	Additional pharmacovigilance information updated to include planned post-authorisation study in MCL patients (Study 3066K1-4438-WW) for risks of infections (including opportunistic), bleeding and mucositis. States status of distribution of the DHPC. Routine risk minimization slightly revised for hepatic impairment to reflect SPC.
Annex 8.5 Newly Available Study Reports	Addition of CSR for Study 3066K1-152-US. Addition of second interim study report from Drug Utilization Study 3066K1-4413-EU.
Annex 8.8 Pharmacovigilance Active Surveillance	Updated document.

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

Discussion on Clinical Safety

When considering the adverse events observed for the higher doses of temsirolimus as compared to the currently authorized dose of 25 mg i.v. weekly, the relatively small database of 108 patients with MCL being exposed to the much higher doses of 175/75mg and 175/25 mg should be taken into account.
Approximately half of these subjects had a dose reduction, and two thirds had a dose delay within the first 3 doses of temsirolimus due to adverse events. Many events were observed with a significantly higher incidence in the temsirolimus 175/75-mg group versus the investigator's choice group ($p<0.05$), the most important differences between treatment groups were thrombocytopenia (72.2% vs 52.8%), asthenia (63.0% vs 26.4%), diarrhea (44.4% vs 9.4%), anorexia (37.0% vs 15.1%), mucositis (35.2% vs 0), rash (35.2% vs 9.4%), epistaxis (35.2% vs 5.7%), infection (27.8% vs 9.4%), pain (27.8% vs 3.8%), cough increased (25.9% vs 9.4%), pruritus (25.9% vs 5.7%), stomatitis (20.4% vs 3.8%), arthralgia (20.4% vs 1.9%), hypokalemia (18.5% vs 0), nail disorder, taste perversion, and upper respiratory infection (14.8% vs 1.9% for each), and dry skin and hypercholesteremia (13.0% vs 0 for each).

Adverse events of special interest were hypersensitivity reactions, haematologic events, thrombotic events, infection-related events, gastrointestinal events, metabolic events, respiratory events and renal events.

Haematologic toxicity was higher in patients with MCL treated with temsirolimus than in RCC (with a recommended much lower dose of temsirolimus 25 mg weekly). This seems not only related to the dose of temsirolimus administered, but also to the included target population of patients with mantle cell lymphoma which were extensively pretreated and included many with bone marrow involvement of the lymphoma. Over 80% of subjects with MCL receiving temsirolimus (in either treatment group) had haematologic TEAEs compared with 39.4% of subjects with RCC receiving 25 mg temsirolimus. Most events of thrombocytopenia were treatment related and grade 3 or 4 in severity, leading to dose delay and dose reduction in a significant number of patients.
Bleeding related TEAEs were reported for 50% and 29.6% in the temsirolimus groups with the majority being epistaxis. The incidences were higher than in the investigator's choice group.

Despite prophylaxis with diphenhydramine or a similar antihistamine, rash was reported in 24.1% in the temsirolimus 175/75-mg group and 16.7% in the temsirolimus 175/25-mg group.
Skin-related TEAEs were reported for a considerable number of patients, i.e. 46.3% and 31.5% of the subjects in the temsirolimus 175/75-mg and temsirolimus 175/25-mg groups, respectively, and in only 11.3% of patients in the investigator's choice arm.

More patients developed increased creatinine in both temsirolimus groups (11.1% and 14.8%, respectively, for the 175/75 mg and 175/25 mg dose group) while this event was not reported for the investigator's choice group.

Infection-related TEAEs were reported in 50.0% and 55.6% of the subjects in the temsirolimus 175/75-mg and temsirolimus 175/25-mg groups, respectively.
The adverse events bronchitis (9.3% and 5.6% for the two temsirolimus arms and 3.8% for the investigator's choice arm) and pneumonia (13% and 28.5% for the temsirolimus arms versus 9.4% for the investigator's choice arms) were considered to be treatment related. Approximately half of the pneumonia and bronchitis events were grade 3 or 4 in severity.
The incidence of mucositis was also clearly much higher in both temsirolimus groups, with a higher incidence in the 175/75 mg group than the 175/25 mg group (mucositis 35% versus 17%), while this adverse event was hardly reported in the investigators' choice group (0% mucositis and 3.8% stomatis).

Hyperlipemia was reported in 9.3% of the 175/75 mg dose group and 20.4% in the 175/25 mg dose group versus 0% in the investigator's choice group. Hypokalemia occurred in 18.5% and 16.7 % of the temsirolimus treated patients (175/75 mg and 175/25 mg dose group respectively) and was not reported in the investigator's choice group.

In comparison to the comparator (investigator's choice) the toxicity was more pronounced in the temsirolimus 175/75 mg group. The choice of rather well tolerated single agents and the use of different agents with different toxicity profiles as well as the shorter time under treatment in the investigator's choice group may have influenced the comparison.

- The incidences of observed toxicity were less for most system organ classes in the investigators choice group.
- The incidence of grade 3 and 4 TEAEs was higher in the temsirolimus groups compared to investigator's choice (88.9% vs. 67.9%).
- The incidence of SAEs was twice as high in the temsirolimus groups (approx. 50 %) compared to investigator's choice (approx. 25 %)
- Although based on small numbers, the number of deaths in the temsirolimus groups are higher for:
    - death due to AE (2 and 3 in the temsirolimus groups vs.. 0 in the investigator's choice group);
    - death due to "other" cause (1 and 3 in the temsirolimus groups vs.. 1 in the investigator's choice group);

    - death within 30 days of first dose (3 and 2 in the temsirolimus groups vs.. 1 in the investigator's choice group);
    - death within 14 days of last dose (4 and 2 in the temsirolimus groups vs.. 1 in the investigator's choice group).
- For more patients in either temsirolimus group than in the investigator's choice group AEs were the reason to discontinue from treatment, for dose delay and dose reductions.
- from the AEs of special interest it is notable that bleeding events, infection-related events, and mucositis related events occurred with a substantially higher incidence in the temsirolimus groups.

Comparing to the known safety profile form the RCC study (25 mg temsirolimus weekly) to temsirolimus 175/75 mg in MCL it is obvious that:

- The same system organ classes are affected.
- However, the toxicity to the haemic and lymphatic system is much more pronounced (TEAE incidence in MCL approx 90 %, RCC approx. 55 %).
- The incidence in grade 3 and 4 TEAEs is higher in MCL (89% vs. 69 %) with a major difference in thrombocytopenia in MCL.
- The incidence in SAEs is higher (approx. 50 % vs. approx.40 %) in MCL.
- The incidences of AEs leading to treatment discontinuation, dose reductions, or dose delays inpatients with MCL receiving temsirolimus 175/75 mg were higher (mainly due to thrombocytopenia, asthenia and dyspnea).
- From the AE of special interest it is notable that in MCL the incidence of bleeding events, infection-related events, and mucositis related events were at least two times higher than in the RCC study.

Overall the toxicity profile shows higher incidences for numerous AEs and ADRs (e.g. thrombocytopenia grade 3 and 4, infections and mucositis) for both temsirolimus arms, which is in accordance with a dose-dependent cytotoxic effect. However, it has to be stressed that the toxicity associated with the proposed posology can hardly be considered mild. For the examples of infections and bleeding events/thrombocytopenia AE incidences were presented by time (first 3 doses and 4^{th} dose onward). The assessment shows that the toxicity adjusted by time is at least doubled compared to investigator's choice consisting of typical cytotoxic treatments, mainly gemcitabine and fludarabine. Moreover, more deaths were reported within the first 30 days on study for both temsirolimus arms. While the benefit is acknowledged and the risk is considered outweighed with reference to the dose of 75 mg weekly, the additional toxicity of the initial doses of 175 mg is obvious without evidence for the contribution of this initial exposure to the global efficacy outcome (see discussion on clinical efficacy).

In summary, the current posology in MCL includes 3 weeks of 175 mg initially that is associated with a higher toxicity in terms of bleeding events, thrombocytopenia and infections than the conventional chemotherapy provided in the investigator's choice group. Although patients in the investigator's choice arm discontinued earlier from study than in the temsirolimus arms, the comparison should be allowed for the first 3 doses (planned for week 1 to week 3).

The incidence of bleeding events /thrombocytopenia and infection is correlated with the high initial dose while the contribution to efficacy of this initial high dose has not been shown (see discussion on clinical efficacy above). The CHMP considers that further investigations are needed to compare the proposed posology with a less toxic regimen (e.g. 75 mg/weekly dose) and to address the question of posology particularly with reference to whether the initial 3 weeks of exposure to 175 mg weekly contribute to the efficacy outcome. As the number of patients in the pivotal study is small, substantially more information on the safety of the two applied doses is considered necessary.

Therefore, upon request by the CHMP, the applicant has committed to conduct a randomised clinical study in patients with MCL to explore whether similar efficacy can be achieved with a less toxic dose regimen, and to evaluate toxic effects of interest further (e.g. bleeding, infection- and mucositis-related events).

The agreed study is a randomized 2-arm trial, which will enrol a total of 100 subjects to receive treatment with either temsirolimus at 175/75 mg (i.e., 175 mg IV per week x 3 doses, followed by 75 mg IV per week) or 75 mg IV given weekly. The primary efficacy objective of this study will be to estimate the hazard ratio (HR) comparing progression-free survival (PFS; as assessed by independent radiological review) between the 2 treatment arms using the Cox Proportional Hazard model. Secondary endpoints will include the estimation of objective response rate (ORR) as well as the estimation of safety profiles (including the prevalence of particular adverse events, such as bleeding, infection and mucositis) for each of the 2 treatment arms.
The MAH will provide the results or this study within agreed timeframes for CHMP review.

Until these data become available and based on the limited information that is assessable now, the SPC and Package Leaflet have been updated with a warning to reflect that the toxicity of the 175 mg dose is substantially more pronounced than the dose authorised for RCC. The SPC highlights that the starting dose of 175 mg was associated with a significant incidence of adverse events and required dose reductions/delays in the majority of patients. Further, the SPC informs prescribers of the fact that the contribution of the initial 175 mg doses to the efficacy outcome is currently not known (see discussion on clinical efficacy above).

Pharmacovigilance

An updated risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- routine pharmacovigilance was adequate to monitor the safety of the product.
- no additional risk minimisation activities were required beyond those included in the product information.

Benefit-risk assessment

In support of this type II variation application to include the indication '*treatment of adult patients with relapsed and/or refractory mantle cell lymphoma (MCL)*', the MAH provided the results of one single pivotal trial (study 3066K1-305-WW); a controlled, randomised, open-label-multicenter, outpatient study comparing 2 different dose regimens of temsirolimus with an investigator's choice. 162 subjects were included and the study was conducted in 15 countries at 108 investigational sites.

Efficacy

Compared with investigator's choice patients receiving temsirolimus 175/75 mg weekly showed an approximately 3 months longer PFS in a study which is considered of high methodological quality (multicentre, multinational, randomised phase 3 study, independent review for the primary endpoint). In this rare indication it is the first study with such a design. The result is statistically significant with a median PFS in the primary analysis of 4.8 and 1.9 months, respectively, HR 0.44 [95 % CI 0.25, 0.78; p=0.0009] and the result is considered robust.

The objective response rate was higher in the temsirolimus 175/75 mg group (22.3 %) compared to the investigator's choice group (1.9 %) supporting the primary endpoint. The ORR indicates that Torisel acts as a cytotoxic agent.

Longer median overall survival time is reported for temsirolimus 175/75 mg compared to investigator's choice: median OS 12.8 months (95% CI, 8.6 to 22.3) and 10.3 months (95% CI, 5.8 to 15.8). However, the difference is not statistically significant: HR 0.78 (CI 0.49, 1.24), p=0.2970.

Safety

Substantially higher toxicity was observed in the MCL study compared to the pivotal study in renal cell carcinoma with a different posology.

The toxicity was more pronounced in the temsirolimus 175/75 group compared to the investigator's choice group (using cytotoxic agents) with respect to the incidences of TEAEs for most system organ classes, as well as the incidence of grade 3 and 4 TEAEs and the incidence of SAEs. Further, the number of deaths in the temsirolimus groups is higher for 'death due to AE', 'death within 30 days of first dose' and 'death within 14 days of last dose' (although based on small numbers) as well as the incidence of AEs leading to discontinuation from treatment, dose delay and dose reductions. Even taking into account the longer time on the experimental treatment a substantial difference has to be noted. The initial doses of 175 mg weekly are accompanied by a substantially higher toxicity including death within 30 days of first dose.

Overall Benefit/Risk

While the benefit is acknowledged and the risk is considered outweighed in respect of the 75 mg IV weekly dose, the additional toxicity of the initial doses of 175 mg is obvious.
Further randomised investigations are required to explore whether similar efficacy can be achieved with a less toxic dose regimen. Further, as the number of patients in the pivotal study is small, substantially more information on the safety of the two applied doses is necessary. The MAH has made a commitment to undertake such a study (see discussion on clinical efficacy and safety above) and provide the results to the CHMP within agreed timeframes for review. Until these data are available this uncertainty needs to be addressed in the SPC, and consequently the SPC has been updated to reflect the fact that the toxicity of the 175 mg dose is substantially more pronounced than the dose authorised for RCC.

An updated risk management plan was provided. The CHMP, having considered the data submitted, was of the opinion that:

- routine pharmacovigilance was adequate to monitor the safety of the product.
- no additional risk minimisation activities were required beyond those included in the product information.

Following the overall assessment of the efficacy and safety data provided, the CHMP concluded that the benefit/risk ratio of Torisel is positive, provided that the requested follow-up measures are undertaken, and agreed on the following final wording of the indication in section 4.1 of the SPC:

"*Mantle cell lymphoma*

*TORISEL is indicated for the treatment of adult patients with relapsed and/or refractory mantle cell lymphoma [MCL], (see section 5.1).****"***

All the proposed consequential changes to sections 4.2, 4.3, 4.4, 4.5, 4.8, 4.9, 5.1, 5.2 and 6.6 of the SPC and the Package Leaflet can be agreed.

Further, the MAH has taken the opportunity to make some minor editorial changes to the annexes and to update the contact details of the UK local representative in the Package Leaflet, which is acceptable.

In addition, the MAH has updated annex IIB to include the version number of the latest Risk Management Plan (version 2.4) agreed with the CHMP.

Furthermore, the CHMP reviewed the data and justifications submitted by the applicant taking into account the provisions of Article 14(11) of Regulation (EC) No. 726/2004, and taking into account the provisions of the "*Guidance on elements required to support the significant clinical benefit in*

comparison with existing therapies of a new therapeutic indication in order to benefit from an extended (11-year) marketing protection period (November 2007)", and considered that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies.

CONCLUSION

On 23 July 2009 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II and Package Leaflet. Furthermore, the CHMP reviewed the clinical data and justifications submitted by the Marketing Authorisation Holder, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considered that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies.