ZELTIA NEWS:

Six new studies presented by PharmaMar (Zeltia Group) at AACR-NCI-EORTC Congress

- **PM01183 (lurbinectedin), PM060184 and Yondelis (trabectedin) are the main compounds analysed in the various trials presented at the 2013 Molecular Targets and Cancer Therapeutics Conference hosted by the American Association for Cancer Research, the National Cancer Institute, and the European Organisation for Research and Treatment of Cancer.**
- **Three of the trials presented analyse a new marine-derived tubulin-binding compound: PM060184. This compound, initially isolated from the sea sponge *Lithoplocamia lithistoides*, is synthesised chemically and is currently in Phase I clinical trials in patients with advanced oncological diseases**

Madrid, 23 October 2013: Six new clinical trials with various products from PharmaMar (biotechnology subsidiary of Grupo Zeltia, MC:ZEL) were presented to oncology specialists and researchers at **the 2013 Molecular Targets and Cancer Therapeutics Conference hosted by the American Association for Cancer Research, the National Cancer Institute, and the European Organisation for Research and Treatment of Cancer.**from 19 to 23 October.

Three of those trials analyse activity in PM060184,a new marine compound that binds to tubulin. PM06184 was discovered and synthesised through PharmaMar's marine drug discovery platform, and was initially isolated from the sea sponge *Lithoplocamia lithistoides*, and later synthesised chemically. The compound is currently undergoing Phase I clinical trials in patients with advanced oncological diseases.

The first trial, "**Mode of action of PM060184, a new interfacial microtubule inhibitor of marine origin**", shows that PM060184 rapidly enters tumour cells, evidencing a high degree of intracellular retention and a high level of avidity for its target, tubulin. Such a stable bond to its intracellular target means that the compound's antitumour effects are practically irreversible. PM060184 inhibits tubulin polymerisation, affecting both interphase cells, where it disrupts the microtubule network and inhibits cell mobility, and mitotic cells, where it induces aberrant mitosis, with multipolar mitosis and lagging chromosomes at the metaphase plate. All these effects correlate with i) prometaphase arrest and induction of classical apoptosis, or ii) the appearance of cells in a multinucleated interphase-like state unrelated to classical apoptosis pathways. These results show that PM060184 is a new anti-microtubule agent with promising potential against cancer.

The second study, "**PM060184 is a new tubulin binding agent that induces strong antitumor activity in xenografted tumors**" reports that, in addition to PM060184's antitumour effect *in vitro* against a broad panel of tumour cell lines, it also evidences powerful in vivo antitumour effects against a panel of five xenografted human tumours: colon, stomach, lung (NSCLC), prostate and kidney. PM060184 was administered intravenously once per week (days 0, 7, 14) for three consecutive weeks at two different doses (8 or 16 mg/kg), with a control group (placebo) in all cases. The results show that treatment with PM060184 induces notable reduction of tumour volume, leading to full tumour regression in colon, gastric and prostate cancers.

The third study, "**The new marine derived tubulin binding agent PM060184 shows potent antitumor activity in vivo against multidrug resistant, Pgp expressing tumors**" used both in vitro and in vivo (xenograft) models of cells that over-express the Pgp pump, a mechanism linked to resistance to treatment with tubulin-binding compounds, such as taxol and vinorelbine. Nevertheless PM060184 retains its powerful antitumour activity (both in vitro and in vivo) regardless of the status of Pgp pump expression.

<u>3 other studies with PharmaMar compounds will be presented at the conference:</u>

"**Collateral sensitivity to cisplatin of trabectedin-resistant cell lines**". This study shows that Soft Tissue Sarcoma cells and Ovarian Cancer Cells become more sensitive to cisplatin as they grow resistant to trabectedin. Resistance is achieved

by repeated treatment with trabectedin until response is critically diminished. Trabectedin resistance is associated with impairment of the NER function, with the consequent increase in cisplatin sensitivity, providing sufficient rationale for testing the sequential combination of trabectedin and platinum complexes in clinical practice. This strategy is being assessed in a patient with ovarian cancer.

"**Comparison of the antitumor activity of trabectedin, lurbinectedin, Zalypsis and PM00128 in a panel of human cells deficient in transcription/NER repair factors**", evidences that marine-based antitumour compounds trabectedin, lurbinectedin, Zalypsis and PM00128 contain a common pentacyclic skeleton that is responsible for the binding to the DNA minor groove. They differ in the remainder of the molecular structure attached to the pentacyclic skeleton that protrudes from the minor groove. The chemical structure of these groups is believed to mediate the compounds' specific interactions with the proteins involved in the various cellular functions, such as DNA transcription and repair. To gain a picture of how the presence of the various chemical moieties may contribute to the compounds' specific activity, their activity profiles were tested against a panel of 24 fibroblast cell lines derived from patients with genetic diseases caused by mutations in the transcription/NER factors CSA, CSB, XPC, XPA, XPE, XPD and XPG.

And finally, **"Analysis of secondary mutations in BRCA1/2 genes as a mechanism of resistance to PM01183 in BRCA-mutation carriers"** analyses possible resistance to PM01183 in BRCA 1/ BRCA 2 carriers. This compound is a modified analogue of trabectedin that binds to the minor groove of DNA by forming adducts (PM01183-DNA) that induce DNA double strand breaks. PM01183 is currently being evaluated in clinical trials, including germline BRCA mutation carriers, since the genomic characterisation of BRCA may provide valuable information for therapeutic decisions and the development of new therapeutic strategies in BRCA carriers. BRCA is a tumour-suppressing gene that regulates the cell cycle and prevents runaway proliferation. The BRCA1 and BRCA2 proteins produced by this gene form part of the system for detecting and repairing DNA double-strand breaks. However, up to 46% of BRCA-associated cisplatin-resistant ovarian tumours and breast cancers with acquired olaparib resistance were found to have secondary BRCA gene mutations which are considered to be the source of resistance to treatment. The hypothesis that BRCA gene reversion (due to

secondary mutation) might be one of the mechanisms of resistance to PM01183 was not confirmed in this study with paired pre- and post-treatment tumour samples. It was observed also that the loss of heterozygosis (LOH) of BRCA does not preclude a response to treatment with PM01183.

About PharmaMar

PharmaMar is a biopharmaceutical subsidiary of GrupoZeltia; it is a world leader in discovering, developing and marketing marine-based drugs to treat cancer. Yondelis® is the first marine-based antitumour drug. PharmaMar has four other compounds in clinical development: Aplidin®, Zalypsis®, PM01183 and PM060184. PharmaMar also has a rich pipeline of pre-clinical candidates and a major R&D programme.

About Zeltia

Zeltia S.A. is a world-leading biopharmaceutical company specialised in the development of marine-based drugs for use in oncology. GrupoZeltia consists mainly of the following companies: PharmaMar, the world-leading biotechnology company in advancing cancer care through the discovery and development of innovative marine-derived medicines; Genómica, Spain's leading company in molecular diagnostics based on DNA analysis; and Sylentis, dedicated to researching therapeutic applications of gene silencing (RNAi).

Important note

PharmaMar, which is headquartered in Madrid (Spain), is a subsidiary of Zeltia, S.A. (Spanish stock exchange: ZEL), which has been listed on the Spanish Stock Exchange since 1963 and on Spain'sElectronic Market since 1998. This document is a press release, not a prospectus. This document does not constitute or form part of an offering or invitation to sell or a solicitation to purchase, offer orsubscribe shares of the company. Moreover, no reliance should be placed upon this document for any investment decision or contract and it does not constitute a recommendation of any type with regard to the shares of the company.

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This note is also available on the PharmaMar web site: www.pharmamar.com and at Zeltia's website: www.zeltia.com