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Investigational anti-cancer drug phenoxodiol produces response and restores chemo-sensitivity in four studies.

Late-breaking Phase 2 prostate cancer study data included at AACR

(Orlando, FL. March 31, 2004 8:00am) Data presented at the 95th Annual Meeting of the American Association for Cancer Research (AACR) in Orlando, Florida, confirms that phenoxodiol is on track in its development as a first-line therapy for early-stage cancers and as a chemo-sensitizing agent for late-stage cancers. Phenoxodiol, a XIAP-inhibitor, is an anti-cancer drug being developed by Marshall Edwards, Inc., (Nasdaq: MSHL). The data presented concerned clinical studies conducted at U.S. and Australian hospitals, and pre-clinical studies conducted at U.S. research institutions.

Interim results of phase 1b/2a data shows dose-related response

Late breaking data from a Phase 1b/2a clinical trial in late-stage prostate cancer patients supports the strategy of targeting this cancer type. Twenty-four patients with malignant prostate cancer and rising prostate specific antigen (PSA) levels (mean 60 ng/mL at start of study) were treated with phenoxodiol (oral dosage formulation) 3 times daily, for 3 weeks each month up to a maximum of 6 months. Patients received 1 of 4 different dosages – 20, 80, 200 or 400 mg. There were 6 patients per dose stratum.

This first trial of oral phenoxodiol was designed to confirm that the dosage form was biologically active. Activity was determined on the basis of PSA levels in the blood. PSA, a protein normally secreted by the prostate, is a marker commonly used to detect the presence of prostate cancer. Although not an absolute predictor of prostate cancer, it is generally accepted that as prostate cancer develops, a greater amount of PSA is released into the blood stream. Objective tumor response was not an aim of this study.

Interim results indicate that oral phenoxodiol is biologically active as evidenced by a dose-dependent effect on serum PSA level. When the 12 patients treated with the 2 highest dosages (200 and 400 mg) were tested after 3 months of therapy, 2 showed stabilization of their PSA levels, while 6 (50%) showed a decrease in PSA levels. Two of these 6 responders showed a decline in PSA levels of greater than 75%. No toxicity was reported.

The clinical study was conducted in Australia by Dr. Robert Davies of Sir Charles Gairdner Hospital in Perth, Professor Alastair Tulloch of St John of God Hospital, Perth, and Dr. Mark Frydenberg of Monash Medical Centre, Melbourne. Co-investigator Dr. Davies said, "Late-stage prostate cancer is notoriously unresponsive to anti-cancer therapies, so to see this degree of response to phenoxodiol confirms our confidence in this investigational drug."

He also said, "While the results of this study suggest that phenoxodiol may be having a significant anti-cancer effect in its own right in prostate cancer, we believe that it has the potential to provide even greater benefit when used in combination with other drugs."

Dr. Graham Kelly, Executive Chairman of Marshall Edwards, Inc., said, "These data justify moving to the next step, which is a larger trial to test for objective tumor response to both phenoxodiol alone and in combination with chemotherapy, in men with late stage prostate cancer."

Yale University study shows monotherapy response in advanced ovarian cancer

The second set of clinical trial data discussed at the conference concerned the intravenous dosage formulation of phenoxodiol. This was a Phase 2 study of monotherapy phenoxodiol in 40 patients with late-stage, unresponsive, recurrent ovarian cancer.

On average, these patients had undergone 5 different chemotherapy regimens, and all patients failed to respond to salvage therapy. The patients were treated with phenoxodiol in an attempt to determine whether phenoxodiol had any anti-tumor effect in such late-stage tumors, and if so, to identify the appropriate dosage to be used in a follow-up study where it would be used in combination with standard chemotoxic drugs.

Intravenous phenoxodiol was administered on 2 consecutive days per week; patients were randomized to 4 dose levels – 1, 3, 10 and 20 mg/kg. Treatment continued until patients showed disease progression. Response to therapy was assessed on the basis of a fall in blood levels of the ovarian tumor marker (CA125), shrinkage of the tumor mass, or improved clinical status.

Ten (25%) of the 40 patients had responded when assessed after 6 weeks of treatment, although tumor mass was not assessed at this time. In 6 of these patients, CA125 levels had fallen by an average 54%; in the other 4 patients, rapidly rising CA125 levels before the trial commenced had stopped rising (stabilization) at 6 weeks. At 3 months, 4 of these 10 patients showed stabilized CA125 levels. Almost all of these responders were in the 2 lowest dosage groups, confirming laboratory studies that showed a greater anti-tumor effect for ovarian cancer at lower dosages for phenoxodiol.

Phenoxodiol restores chemo-sensitivity in patients with advanced ovarian cancer

Relevant data, however, in terms of the company strategy of developing phenoxodiol as a chemo-sensitizing agent for late-stage cancers, came from the follow-up management of these patients. Following completion of the phenoxodiol therapy because of disease progression, a number of the patients were re-challenged with standard chemotoxic drugs in order to test what effect phenoxodiol therapy had on their sensitivity to standard anti-cancer drugs. Because all patients had recurrent disease despite being heavily treated with chemotherapy, a clinical response to further chemotherapy was considered unlikely.

In 10 patients who received paclitaxel, 8 of the 10 responded with an immediate and marked decline (average 64%) in their CA125 levels; the other 2 women failed to respond and showed progressive disease. Five of the 10 women treated with paclitaxel were previously considered either resistant or refractory to paclitaxel (that is, their disease previously either had recurred within 6 months of paclitaxel therapy, or continued to worsen despite paclitaxel therapy). However, after treatment with phenoxodiol and subsequent treatment with paclitaxel, 4 of these 5 patients showed a marked response in their CA125 levels, and 3

remain alive after an average of 292 days. These patients have yet to be assessed radiographically to determine the degree of objective tumor response.

Dr. Thomas Rutherford of the Yale University School of Medicine, and Principal Investigator in the study, said, "we are excited that phenoxodiol has been able to provide an effect in women whose disease has been so heavily pre-treated and for whom we have run out of options".

"But we have always believed that the best way to use the drug was as a chemo-sensitizer, restoring the cancer cell's susceptibility to standard drugs once they have become resistant to those drugs," Rutherford added. "That is why this preliminary finding with phenoxodiol and paclitaxel is so exciting. We have seen women positively respond to paclitaxel after being pre-treated with phenoxodiol despite their earlier resistance to paclitaxel."

Dr. Kelly said, "This trial represents the first stage of a two-part program to develop phenoxodiol as a chemo-sensitizer in ovarian cancer patients. The trial has been successful in helping us identify an appropriate, well-tolerated dose of 3 milligrams per kilogram."

Laboratory data from Yale shows phenoxodiol restores chemo-sensitivity to a broad range of chemotherapy

In a pre-clinical study conducted by Yale University and reported on by Gil Mor M.D., Associate Professor, Department of Obstetrics and Gynecology, phenoxodiol was shown to restore sensitivity in ovarian cancer cells not only to taxane drugs such as Taxotere® (docetaxol), but also to platinum agents such as carboplatin. Additionally, phenoxodiol in combination with gemcitabine had a comparable response. Significantly, ovarian cancer cells resistant to each of these cytotoxic drugs showed an over 100-fold increase in their sensitivity to chemotherapy following pre-treatment with phenoxodiol.

Dr. Mor said, "What makes the results of this laboratory study so significant is the confirmation that phenoxodiol has the capacity to reverse chemo-resistance in ovarian cancer patients".

"Chemo-resistance is one of the greatest problems we face in cancer therapy. Almost every patient with advanced ovarian cancer ultimately becomes resistant to all anti-cancer drugs. We believe that phenoxodiol is a tool to overcome this problem so we can offer these patients renewed hope."

NIH laboratory study shows phenoxodiol kills head and neck cancer cells

In an additional pre-clinical study conducted by the NIH and reported on at the conference, the means by which phenoxodiol was able to stop head and neck cancer cells (squamous cell carcinomas) from growing, was described. Of particular relevance, however, was the fact that phenoxodiol was able to stop the growth in the laboratory of head and neck cancer cells and salivary gland cancer cells that were highly resistant to standard anti-cancer drugs.

Mechanisms of action: phenoxodiol induces apoptosis by disrupting intra-cellular proteins

Phenoxodiol has been developed as a highly selective inducer of apoptosis in tumor cells that works by removing the intra-cellular proteins (XIAP, c-FLIP) that play a major role in ensuring the survival of cancer cells. Removal of these proteins has the dual effect of rendering the cancer cell susceptible to the body's normal defense mechanisms as well as

making it more sensitive to the cytotoxic effects of standard anti-cancer drugs. The highly selective nature of phenoxodiol means that the drug has no discernible adverse effects on non-tumor cells, and its ability to enhance the killing effect of other chemotoxics is restricted to tumor cells.

Marshall Edwards, Inc., is developing phenoxodiol on two broad therapeutic strategies. First, as a first-line therapy for early-stage cancer (including prostate and cervical cancers) where early detection is possible, and where the cancer is particularly prone to the apoptotic effect of phenoxodiol alone. Second, as a first-line therapy for late-stage cancers (including prostate carcinoma and renal carcinoma) to improve the responsiveness to standard chemotoxics in cancers that are intrinsically poorly sensitive to such drugs, or as a second-line therapy to restore responsiveness to standard chemotoxics in cancers (including ovarian carcinoma) that have acquired resistance to such drugs.

Phenoxodiol has IND status within the U.S. and has not yet been evaluated by the FDA for marketing approval.

Phenoxodiol, an investigational anti-cancer drug developed by pharmaceutical company, Marshall Edwards, Inc. Marshall Edwards, Inc., manages its international research and development programs using the expertise and clinical research capabilities of universities and hospitals in the U.S., Australia and Europe.

Marshall Edwards, Inc., has licensed rights to bring phenoxodiol to market globally from its parent company, Novogen Limited. (Nasdaq: NVGN). Novogen is developing a range of therapeutics across the fields of oncology, cardiovascular disease and inflammatory diseases based on its phenolic drug technology platform.

More information on phenoxodiol and on the Novogen group of companies can be found at www.marshalledwardsinc.com and www.novogen.com.

Statements included in this press release that are not historical in nature are "forward-looking statements" within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995. You should be aware that our actual results could differ materially from those contained in the forward-looking statements, which are based on management's current expectations and are subject to a number of risks and uncertainties, including, but not limited to, our failure to successfully commercialize our product candidates; costs and delays in the development and/or FDA approval, or the failure to obtain such approval, of our product candidates; uncertainties in clinical trial results; our inability to maintain or enter into, and the risks resulting from our dependence upon, collaboration or contractual arrangements necessary for the development, manufacture, commercialization, marketing, sales and distribution of any products; competitive factors; our inability to protect our patents or proprietary rights and obtain necessary rights to third party patents and intellectual property to operate our business; our inability to operate our business without infringing the patents and proprietary rights of others; general economic conditions; the failure of any products to gain market acceptance; our inability to obtain any additional required financing; technological changes; government regulation; changes in industry practice; and one-time events. We do not intend to update any of these factors or to publicly announce the results of any revisions to these forward-looking statements.