



North America  
Europe  
Australasia

## Protherics PLC

### Prolarix™ dose selected for phase 2 liver cancer study

**London, UK; Brentwood, TN, US; 12 July 2007** - Protherics PLC ("Protherics" or the "Company"), the international biopharmaceutical company focused on critical care and cancer, today announces the maximum tolerated dose ("MTD") of Prolarix™ has been determined in a phase 1 study being conducted under the auspices of Cancer Research UK. Prolarix™ is a novel targeted prodrug therapy being developed for the treatment of primary liver cancer (hepatocellular carcinoma) and other selected tumours.

Treatment with Prolarix™ involves the co-administration of two small molecules: a prodrug, tretazicar, which is activated by an endogenous enzyme called NQO2 in the presence of a cosubstrate, caricotamide. The dose of caricotamide was fixed early in the study, while the dose of tretazicar was escalated until the MTD was determined. Twenty three patients have been treated in the study to date, and activation of the prodrug has been indicated in all patients where pharmacokinetic analyses have been performed.

Six additional patients with a range of tumour types will now be treated with up to six cycles of Prolarix™ at the MTD to further investigate drug effects in the tumour, safety and to make a preliminary assessment of potential efficacy. Patients will have tumour biopsy samples taken once they have been enrolled in the study to determine tumour NQO2 levels and the pharmacodynamic effects of Prolarix™.

Cancer Research UK is expected to report the study in the first half of 2008. Meanwhile, Protherics is planning to start a phase 2 proof of concept study in the first half of 2008 to investigate the efficacy of Prolarix in primary liver cancer, where NQO2 levels have been found to be elevated.

Andrew Heath, Chief Executive of Protherics commented:

"Prolarix™ is a novel prodrug based cancer therapy with great potential in the treatment of primary liver cancer. We look forward to investigating its effects in this difficult to treat cancer in a phase 2 study next year."

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## **Notes for Editors:**

### **About Prolarix™**

Prolarix is a targeted chemotherapy being developed for the treatment of primary liver cancer (hepatocellular carcinomas, HCC) and other select tumours. Prolarix is a combination therapy of two low molecular weight compounds, a prodrug\* (called tretazicar; previously CB1954) and an enzyme co-substrate\* (called caricotamide; previously EP-0152R).

The prodrug tretazicar can be activated, by an endogenous enzyme called NQO2, to a highly reactive, short-lived cytotoxic agent which causes a high degree of DNA cross-linking. The NQO2 enzyme is latent and therefore inactive in body tissue, but Protherics' scientists have discovered that the enzyme is active in the presence of a co-substrate called caricotamide.

The NQO2 enzyme is absent or in low levels in many normal body tissues, including bone marrow, but its activity is increased in certain tumour types (particularly hepatocellular carcinomas). The coadministration of the prodrug tretazicar, and the cosubstrate, caricotamide, is therefore expected to result in the enhanced activation of the prodrug in the target tumour cells, resulting in their death while minimising harm to healthy, non-cancerous cells.

### **Glossary**

**Prodrug\*** - A compound that is converted within the body into its active form and that has no therapeutic effects of its own. A prodrug is useful when the active drug may be too toxic to administer systemically, the active drug is absorbed poorly by the digestive tract, or the body breaks down the active drug before it reaches its target.

**Co-substrate\*** - A molecule that interacts with an enzyme and is required for its activity.

**Cytotoxic\*** - A chemical which has a direct toxic effect to cells, causing their death.

**Tretazicar\*** is 5-(aziridin-1-yl)-2,4-dinitrobenzamide (CB 1954), an antitumour prodrug

**Caricotamide\*** is 1-carbamoylmethyl-3-carbamoyl-1,4-dihydropyridine (EP-0152R), the most stable of a series of co-substrates discovered by Protherics

### **About Protherics**

Protherics (LSE: PTI, NASDAQ: PTIL) is a leading biopharmaceutical company focused on the development, manufacture and marketing of specialised products for critical care and cancer.

Protherics has developed and manufactures two biologics for critical care which are FDA approved and currently sold in the US: CroFab™, a pit viper antivenom and DigiFab™, a digoxin antidote. The Company's strategy is to use the revenues generated from its marketed and out-licensed products to help fund the advancement of its broad, late stage pipeline.

Protherics has two major development opportunities in its critical care portfolio. CytoFab™ is being developed by AstraZeneca, for the treatment of severe sepsis, after a major £195 million (\$340 million) licensing deal with AstraZeneca in December 2005. An additional, expanded phase 2 programme is planned to start in the second half of 2007. In addition, Protherics is currently undertaking a phase 2b study with Digoxin Immune Fab for the treatment of pre-eclampsia. This study is expected to report in the first half of 2008.

Protherics has a pipeline of four novel cancer products in clinical development, and intends to undertake the sales and marketing of these products in the US and EU. Protherics is preparing to resubmit a BLA for Voraxaze™, an adjunct to high dose methotrexate therapy, under a rolling submission in the US starting in early 2008.

Protherics has a strong cash position, having completed a £38 million equity fundraising in January 2007 and received a £10 million milestone payment from AstraZeneca in April 2007.

With headquarters in London, the Company has approximately 270 employees across its operations in the UK, US and Australia.

For further information visit: [www.protherics.com](http://www.protherics.com)

**Disclaimer**

This document contains forward-looking statements that involve risks and uncertainties including with respect to future growth, product development and clinical studies, receipt of milestone payments, product sales and regulatory approval of Protherics' products for marketing and distribution. Although we believe that the expectations reflected in such forward-looking statements are reasonable at this time, we can give no assurance that such expectations will prove to be correct. Given these uncertainties, readers are cautioned not to place undue reliance on such forward-looking statements. Actual results could differ materially from those anticipated in these forward-looking statements due to many important factors, including the market for the Company's products, the timing and receipt of regulatory approvals, the progression and results of clinical studies, the successful integration of acquired businesses and intellectual property, and other factors discussed in Protherics' Annual Report on Form 20-F and other reports filed from time to time with the U.S. Securities and Exchange Commission. We do not undertake to update any oral or written forward-looking statements that may be made by or on behalf of Protherics.