PRESS RELEASE

PANTARHEI ONCOLOGY ANNOUNCES FAVORABLE EFFICACY RESULTS OF THE FETAL ESTROGEN ESTETROL IN WOMEN WITH ADVANCED BREAST CANCER

Zeist, the Netherlands, 6 December 2018

On Friday 7 December 2018 the first positive results of the treatment of advanced breast cancer with the fetal estrogen Estetrol will be presented at the San Antonio Breast Cancer Symposium (SABCS) in the USA. In the clinical ABCE4 (Anti Breast Cancer Estetrol) study in Germany, objective anti-tumor effects are observed in two of the first three patients treated with high dose Estetrol.

Since 1944, synthetic and natural estrogens have been successfully used for the treatment of breast cancer, especially in women who were more than 5 years postmenopausal. However, in the 19sixties the estrogens were replaced by anti-estrogens, because of perceived higher toxicity of estrogens, especially cardiovascular side effects, although anti-estrogens carry increased cardiovascular risks too. Estrogens can be effective for the treatment of advanced breast cancer, provided the patients are postmenopausal and have developed resistance to anti-estrogen treatment. Therefore, in the ABCE4 study, apart from having an estrogen receptor positive (ER+) locally advanced and/or metastatic breast cancer, criteria for treatment with Estetrol are a postmenopausal status of at least 5 years, proven resistance to anti-estrogen treatment and no further treatment options available.
At present all patients with ER+ advanced breast cancer are treated with anti-estrogenic drugs such as tamoxifen, aromatase inhibitors and fulvestrant, increasingly in combination with CDK 4/6 inhibitors. However, over time, patients become resistant to the anti-estrogen therapy, whereas the majority of these patients have symptoms of serious estrogen deficiency with subjective symptoms such as arthralgia, frequent hot flushes, dryness of the vagina and problems with sexual intercourse, mood changes and depression, sleeping problems and objective signs such as bone loss, fractures and cognition problems.

Therefore, the second major outcome parameter of the ABCE4 study is the effect of Estetrol on subjective complaints related to estrogen deficiency and thereby on quality of life. All three patients treated so far with 20 mg Estetrol per day reported a remarkable improvement of quality of life. At present three patients are in the initial phase of treatment with 40 mg Estetrol per day without dose limiting toxicity so far and a too short treatment period to judge efficacy.

Prof Marcus Schmidt from the Johannes Gutenberg University in Mainz, Germany and the principal investigator of the ABCE4 study: "Apart from being happy with the positive effect on the tumor, patients are feeling much better and especially less depressed with Estetrol. Quality of life is becoming increasingly important in the choice of medical treatment of breast cancer and Estetrol is well positioned to qualify as the first choice treatment after anti-estrogen resistance has developed and before progressing to the more toxic cytostatics"

Herjan Coelingh Bennink, CEO Pantarhei Bioscience and Pantarhei Oncology, commented: "Since the discovery of Estetrol as a new drug by Pantarhei Bioscience in 2001, this mysterious estrogenic hormone, occurring during human pregnancy only, has pleasantly surprised us again and again and now we find that breast tumors disappear with high doses of Estetrol. Whereas other natural estrogens are broken down by the liver and may interfere with liver function, causing an increased risk of thrombosis, Estetrol hardly interacts with the liver and is therefore expected to be safer for the cardiovascular system, whereas adequate blood levels can be obtained by once-a-day oral administration.
Based on our preclinical and clinical research from 2001-2015, we expected a favourable effect on advanced breast cancer. We are excited that the first clinical results presented this week at the important breast cancer symposium in San Antonio support the expected efficacy of Estetrol on tumor growth. The beneficial effects on quality of life and well-being of these seriously estrogen deficient patients are no surprise for us. Although the ABCE4 study is still ongoing with higher doses of Estetrol, the positive results of the 20 mg dose group already qualify this dose for further development. At present the costs of new drugs are a hot topic. Although the synthesis of Estetrol is rather complicated, the final product may become reasonably priced "

About Estetrol and Pantarhei Bioscience

Estetrol is a fetal estrogen, synthesised by the human fetal liver during pregnancy only. It is also known as E4, referring to the four OH groups in the steroid molecule. Estetrol was first identified by the group of Egon Diczfalusy in 1965 at the Karolinska Institute in Stockholm, Sweden.
Since 2001 Pantarhei Bioscience has performed extensive preclinical pharmacological studies with E4, followed by phase I and phase II safety, efficacy and dose finding studies in human volunteers to develop E4 as the estrogen in an oral contraceptive (OC) and for menopausal hormone therapy (MHT).
In 2015 Pantarhei Bioscience sold its E4 portfolio to the Belgian company Mithra Pharmaceuticals for further OC and MHT development and founded a subsidiary company Pantarhei Oncology for the development of oncological applications of E4 with special emphasis on breast and prostate cancer. Mithra has selected a daily dose of 15 mg E4 for both the OC and the MHT application. Recently, Mithra reported the first results of their phase III OC program with daily exposure of more than 3500 women to 15 mg E4 without relevant safety problems.

About Pantarhei Oncology

Pantarhei Oncology (PRO) is a Dutch biotechnology company focussing on the development of innovative concepts for hormone-related cancer treatment. PRO develops patent protected new

treatment concepts up to proof-of-concept (PoC) in the human (phase II). At present PRO is involved in clinical safety and PoC studies with Estetrol in breast cancer and prostate cancer patients and in the preclinical development of a new immunotherapy, based on the use of the natural antigen Zona Pellucida 3 (ZP3) for cancers expressing ZP3. The first encouraging results of the ongoing breast cancer study in Germany are summarised in this press release. In the Netherlands a double-blind, placebo-controlled PoC study is ongoing in men with advanced prostate cancer, treated with an LHRH agonist, combined with 40 mg E4 per day or placebo. Results are expected late 2019.

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