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## Antisense gets South Korean & Taiwanese nod for studies using anti-cancer drug trabedersen in brain tumour

Regensburg  
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The biopharmaceutical company Antisense Pharma announced that the South Korean health agency KFDA as well as the Taiwanese health agency TFDA has granted their approvals for the implementation of clinical studies using the anti-cancer drug trabedersen for patients with high-grade brain tumours. Trabedersen is a gene-silencing substance inhibiting the tumour factor Transforming Growth Factor beta 2 (TGF- $\beta$ 2) at its translational level.

The efficacy and tolerability of trabedersen for high-grade glioma has already been demonstrated during a randomized and actively controlled phase II b study. The substance is currently also in clinical development for indications such as advanced pancreas carcinoma, malignant melanoma and colorectal carcinoma. The involvement of Southeast Asian countries for clinical testing of trabedersen is part of Antisense Pharma's strategic development programme for the global marketing of this compound. Including South Korea and Taiwan, a total of 13 countries are now participating in the international pivotal study.

High unmet need for medical innovations for patients with highly malignant glioma the randomized and actively controlled phase III study Sapphire is scheduled to begin at selected medical centres in South Korea and Taiwan during the first quarter of 2011. The medical demand for therapies against high-grade brain tumours remains to be high: according to the World Health Organization (WHO), Southeast Asia annually has more than 13,000 incident cases of central nervous system tumours, with a mortality rate of more than 77 per cent. "Our pivotal phase III study not only meets the enormous interest in trabedersen of South Korean and Taiwanese physicians, who just as their colleagues from all over the world have so far no satisfactory medical treatment to provide to their critically ill patients suffering from high-grade brain tumours", explains Dr Karl Hermann Schlingensiepen, chief executive officer of Antisense Pharma.

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“The global involvement of neurosurgeons and neurooncologists for the clinical development of trabedersen also allows us to introduce them to our completely new therapy concept at an early stage. This means that by the time trabedersen will be launched, these doctors will be familiar with the concept and can leverage their clinical practice experience” he further added.

Smooth approvals by KFDA and TFDA “The excellent exchange with the regulatory authorities in South Korea and Taiwan has led to a prompt granting of approvals, thus confirming the professional work of our team and Antisense Pharma’s expertise in clinical drug development”, comments Dr Hubert Heinrichs, chief medical officer of Antisense Pharma. “Key factors for the decision taken by KFDA and TFDA have surely been the very encouraging results of previous clinical studies which confirm the safety, tolerability and efficacy of trabedersen.”

Antisense Pharma receives approval for clinical studies in South Korea and Taiwan in malignant brain tumours. With this approval, the Southeast Asian health agencies KFDA and TFDA have paved the way for the implementation of the pivotal phase III study Sapphire with the TGF- $\beta$ 2 inhibitor trabedersen

Trabedersen is a first-in-class gene silencing anti-sense compound - a phosphorothioate oligodeoxynucleotide – designed to selectively down regulate the production of Transforming Growth Factor-beta 2 (TGF- $\beta$ 2) at the translational level. TGF- $\beta$ 2 plays a pivotal role as a multimodal cytokine by regulating key mechanisms of tumour progression. Immunosuppression, invasion and metastasis, proliferation and angiogenesis are simultaneously promoted by TGF- $\beta$ 2 in a variety of malignant tumours.

Therefore Trabedersen is a targeted multimodal therapy and one of the very promising immunotherapeutic approaches in the oncological field. Besides in high grade glioma, trabedersen is also being investigated in other aggressive cancers which over-express TGF- $\beta$ 2: Trabedersen is being systemically administered intravenously (i.v.) in adult patients with advanced pancreatic carcinoma, malignant melanoma, or advanced colorectal carcinoma in an ongoing phase I/II study.

Anaplastic Astrocytoma (AA) and Glioblastoma Multiforma (GBM) are the two most common forms of primary brain tumours and are diseases with high unmet medical need. Adults as well as children may be affected, although the peak age is 45-65 years. Current therapies comprise surgery, radiation and/or chemotherapy. Despite recent advances, the prognosis for these patients is still poor, with a high proportion dying within two years after initial diagnosis. Antisense Pharma is the sponsor of the pivotal international Sapphire clinical phase III study, investigating the efficacy and safety of trabedersen (AP 12009) in adult patients.

The completed clinical phase IIB study AP 12009-G004 was an open-label, randomized, active-controlled, parallel-group dose finding study to evaluate the efficacy and safety of two doses of trabedersen (AP 12009) in adult patients with recurrent or refractory high-grade glioma. At 29 international clinical centres, 134 evaluable patients (39 with recurrent or

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refractory AA, WHO grade III and 95 with recurrent or refractory glioblastoma, GBM, WHO grade IV) were randomized to three arms: 10 -M trabedersen, 80 - M trabedersen or standard chemotherapy (temozolomide or PCV) as active control.

Analysis of the core phase revealed long-lasting tumour responses and life extension in AA and GBM patients, by far exceeding the active treatment period with trabedersen. For recurrent or refractory Anaplastic Astrocytoma patients, median survival times in the 10 -M trabedersen group were 39.1 months compared to 21.7 months in the standard chemotherapy control arm, translating to a survival benefit of 17.4 months for patients receiving the Antisense treatment over standard chemotherapy. 83.3% of the patients with recurrent anaplastic astrocytoma who received 10 -M trabedersen survived two years or more, whereas only 41.7% survived two years in the control arm with standard chemotherapy.

Both efficacy and safety results have demonstrated, that the 10 -M concentration of trabedersen was superior to the 80 -M concentration. This further underlines the specificity of this targeted therapy since for optimally targeted therapies maximum tolerated dose is not necessarily the most efficient dose. This data have been published in the official journal of the American Society for NeuroOncology (SNO) in 2010 (Bogdahn U et al. Targeted therapy for high-grade glioma with the TGF- $\beta$ 2 inhibitor trabedersen: results of a randomized and controlled phase IIb study.

Antisense Pharma focuses on targeted therapies for malignant tumours and is dedicated to discovering and developing drugs based on antisense technology for worldwide commercialization. The medications specifically block the synthesis of key cancer proteins.