



Press Release

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Clinical Proof of Concept for TGF-beta 2-Inhibitor AP 12009 in Phase IIb EMA provides Guidance on Phase III Design and Approval Requirements

CHICAGO/REGENSBURG - June 2, 2008 - "A two-year survival rate of more than 80 percent in recurrent or refractory anaplastic astrocytoma suggests a breakthrough in this devastating disease by targeted therapy," commented Prof. Ulrich Bogdahn, Neuro-Oncologist and Coordinating Investigator of the Phase IIb active-controlled dose-finding trial with AP 12009 in recurrent or refractory high-grade glioma, while presenting the data at the 44th Annual Meeting of the American Society of Clinical Oncology (ASCO) in Chicago, USA, today. The 24-month survival rate was accepted by the Scientific Advice Working Party (SAWP) at the EMA as the primary endpoint for the upcoming Phase III study in recurrent or refractory anaplastic astrocytoma patients. Furthermore, 14-month progression rate was accepted as the endpoint for conditional approval.

The drug designed for the targeted treatment of recurrent or refractory high-grade glioma was administered as monotherapy and compared to standard chemotherapy in an international, randomized, active-controlled Phase IIb clinical trial. Efficacy results show that the 10 μ M dose of AP 12009, identified in the Phase IIb trial, is superior to standard chemotherapy in anaplastic astrocytoma: Current median survival times in the 10 μ M AP 12009 group are 37.2 months compared to 21.7 months in the standard chemotherapy control arm. This translates to a survival benefit of 15.5 months for patients receiving the antisense treatment over chemotherapy. In recurrent or refractory anaplastic astrocytoma, 83.3% of the patients treated with 10 μ M AP 12009 survived two years or more, whereas 41.7% survived in the control arm with standard chemotherapy (1).

"The effect of the drug is long-lasting and by far exceeds the period of active treatment," said Prof. Bogdahn, Director of the Department of Neuro-Oncology, University of Regensburg. This is fully supported by a steady increase in overall tumor response rates for 10 μ M AP 12009 in recurrent or refractory anaplastic astrocytoma, with up to 42% at 14 months. At the same time, the initial 25%-overall response rate in the control group fell to zero.

An international, randomized, active-controlled, Phase III study to evaluate the efficacy and safety of AP 12009 as monotherapy in adult patients with recurrent or refractory anaplastic astrocytoma will start in Q3 2008. The study drug will be compared to standard chemotherapy with either Temozolomide or BCNU. Antisense Pharma plans to conduct an interim analysis using the progression rate at 14 months as the surrogate endpoint. Positive results will allow submission for conditional approval by the EMA. The SAWP at the EMA indicated that, due to the rarity of the disease, the surrogate endpoint would be accepted, provided that the response data are supported by survival data.



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The fixed timepoint analysis at 24 months will be acceptable as the primary endpoint for full approval. Furthermore, a time-to-event analysis will be performed. "We are very pleased with this explicit statement by the Scientific Advice Working Party to proceed as we have planned. We sincerely hope that this will accelerate access to treatment for patients in need," says Dr. Hubert Heinrichs, Chief Medical Officer of Antisense Pharma. The Phase III study aims to enroll recurrent or refractory anaplastic astrocytoma patients in about 50 centers in 12 countries.

In the international randomized, active-controlled Phase IIb study, reported at ASCO, recurrent or refractory glioblastoma patients also showed long-lasting tumor responses in the AP 12009 groups (2). As of April 2008 the odds ratio for 10 μ M AP 12009 versus control is 0.54. The risk to die is thus reduced by approximately 50% for glioblastoma patients receiving the study drug, as compared to patients under standard chemotherapy treatment. "Based on these data, a pivotal clinical trial in glioblastoma patients with good prognosis, for example newly diagnosed, is scheduled to start in 2009," explains Dr. Karl-Hermann Schlingensiepen, Chief Executive Officer of Antisense Pharma.

Literature

- (1) Bogdahn, U. et al. "Results of a Phase IIb Active-controlled Study with AP 12009 for Patients with Recurrent or Refractory Anaplastic Astrocytoma", ASCO Annual Meeting, 2008, Abstract ID 2076
- (2) Bogdahn, U. et al. "Targeted Therapy with AP 12009 in Recurrent or Refractory Glioblastoma Patients: Results of a Phase IIb Study", ASCO Annual Meeting, 2008, Abstract ID 2018

The Phase IIb study AP 12009-G004

The Phase IIb study AP 12009-G004 is an open-label, randomized, active-controlled, parallel-group dose-finding study to evaluate the efficacy and safety of two doses of AP 12009 in adult patients with recurrent or refractory high-grade glioma. Efficacy endpoints were tumor response assessed by central blinded MRI reading and survival. At 29 international clinical centers, 134 evaluable patients (39 with anaplastic astrocytoma, AA, WHO grade III and 95 with glioblastoma, GBM, WHO grade IV) have been randomized to three arms: AP 12009 10 μ M, AP 12009 80 μ M and standard chemotherapy (Temozolomide or PCV) as an active control. AP 12009 was administered intratumorally via one catheter as continuous high-flow microperfusion over a 7-day period every other week for up to 6 months on an outpatient treatment basis. Tumor response was assessed according to Macdonald criteria. Post-study follow-up for survival, long-term tumor response, and safety is still ongoing. Analysis of the core phase is completed.



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AP 12009 and TGF-beta 2

AP 12009 is an antisense drug - a phosphorothioate oligodeoxynucleotide - designed to selectively downregulate 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 tumor progression. Immunosuppression, invasion and migration, proliferation and angiogenesis are simultaneously promoted by TGF-beta 2 in a variety of malignant tumors. This multiple impact on cancer cells is inhibited by AP 12009.

High-Grade Glioma

Anaplastic astrocytoma and glioblastoma are the two most common forms of primary brain tumors, a diagnosis with high unmet medical need. Adults as well as children may be affected, although the age peak is at 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 of initial diagnosis.

About Antisense Pharma GmbH

Antisense Pharma is a biopharmaceutical company located in Regensburg, Germany. The company focuses on targeted therapies for malignant tumors and is dedicated to discovering and developing drugs based on antisense technology for worldwide commercialization. The agents specifically block the synthesis of key cancer proteins. Antisense Pharma has been honored with the Bavarian Innovation Award and the German Founders Award.

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