ANG1005, the first clinical trial in patients with malignant glioma: Preliminary safety and tolerability data

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UPATED ABSTRACT

Treatment options for recurrent malignant gliomas are limited and prognosis is dismal mostly due to the presence of the BLOOD-BRAIN BARRIER (BBB) which prevents most cancer drugs from reaching tumor cells in the brain. Angiopep-2 is a 19 amino acid peptide shown in animal models to cross the BBB using a physiological approach via transcytosis by binding to low-density lipoprotein receptor-related protein (LRP) expressed on the surface of the BBB. ANG1005 is a new chemical entity (NCE) that combines one molecule of Angiopep-2 with three molecules of paclitaxel. Preclinical studies demonstrate the brain's uptake of ANG1005 is up to 100% greater than that of LRP. Once inside the brain, ANG1005 enters tumor cells using the same receptor-mediated pathway described above, through LRP, which is upregulated in various cancer cells including malignant glioma cells. The clearance of plasma is lower when compared to LRP because Angiopep-2 is broken down by esterase in the lysosomes of the cells releasing paclitaxel which has been shown to retain its antimitotic activity. A multicenter, open-label, dose escalation study of ANG1005 was initiated in October 2007 to explore the maximum tolerated dose and obtain data on safety, tolerability, and preliminary evidence of efficacy in patients with recurrent malignant gliomas. The dose escalation scheme includes sequential dose cohorts ranging from 30 to 105 mg/m². ANG1005 is administered IV every 21 days with weekly safety visits. Study participants are adult patients with measurable disease and an ECOG performance status no worse than 2 who are ineligible for standard treatment options. As of Nov 3, 2008, 17 patients with recurrent malignant glioma have been treated (10 patients with glioblastoma multiforme, 7 with anaplastic astrocytoma, 5 with anaplastic oligodendrogloma and 3 with oligoastrocytoma). No patient has discontinued from the study due to study drug-related adverse events. The currently enrolling dose is 105 mg/m² and escalation is ongoing. Angiopep-2 may represent a potentially safe and effective way to treat presently unmanageable CNS disorders. ANG1005 is the first of a list of compounds to be tested in this regard.

INTRODUCTION

The BLOOD-BRAIN BARRIER prohibits more than 95% of drugs from reaching the site of disease located in the brain, such as brain cancer.

• It is vital that approaches be found that allow therapies access to the brain compartment.
• The scientific community recognizes distinct advantages of physiological approaches.
• The research presented herein is based on a physiological approach and the observation that most molecules that reach the brain must interact with specific receptors via active transport.

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Paclitaxel and other chemotherapeutics have limited use in brain cancers due to their inability to penetrate the BBB in sufficient quantities. Preclinical studies show that brain uptake of ANG1005 is 100% greater than paclitaxel and that once in the brain compartment, ANG1005 favorably targets tumor cells which it enters by endocytosis using the same receptor mechanism. Inside tumor cells, the esterase linkages that bind paclitaxel to Angiopep-2 are cleaved by esterase, found in high concentration in the lysosomes of the cells. Furthermore, the therapeutic properties of paclitaxel have been shown to be conserved once it dissociates from Angiopep-2.

Because of strong preclinical data, ANG1005 entered the clinical phase of development late last year. The present Phase I dose-finding study represents the first time ANG1005 is being administered to patients with recurrent malignant gliomas, the most common and aggressive primary brain cancers.

MATERIALS AND METHODS

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PATIENT PROFILE:

Results presented here include data up to and including November 3, 2008. 17 patients with recurrent malignant glioma (10 with Glioblastoma Multiforme, 1 with Anaplastic Astrocytoma, 5 with Anaplastic OligoDendrogloma and 3 with OligoAstrocytoma) have received ANG1005 at doses ranging from 30 to 105 mg/m²; escalation is ongoing.

SAFETY DATA:

Safety data are available for all 17 study patients dosed to date.

RESULTS

Three infusion reactions (2 Grade 2, 1 listed above, and 1 Grade 1) have been observed; all occurred within the first few minutes of the infusion – in 2 cases the reactions were seen during cycle 1 while in the other case the reaction occurred during the second cycle of treatment. Due to the reactions, the infusions were interrupted and the patients were treated with success allowing the infusions to be completed.

No patient has discontinued from the study due to study drug-related AEs.

Preliminary pharmacodynamic data show that ANG1005 does not affect cognitive performance at these doses in this population. Furthermore, immunogenicity data to date indicate that ANG1005 does not elicit an immune response.

TUMOR RESPONSE DATA:

6-week tumor response data is available for 10 patients. Although efficacy is not expected at the low doses used thus far, 6-week data reveal 1 minor response (~10% decrease) in a GBM patient dosed at 30 mg/m² and 2 stable diseases – one in a GBM patient dosed at 75 mg/m² and one in a patient with anaplastic oligodendroglioma dosed at 105 mg/m².

CONCLUSIONS:

• Existing drug candidates (mostly biologic) available to address conditions localized in the brain have limited to no therapeutic value in vivo due to the fact that they do not penetrate the BBB to reach the site of disease.

• In an effort to overcome this obstacle, Angiochem has developed a new vector technology based on chemically attaching small molecules, peptides, monoclonal antibodies, siRNA, etc. to a vector that shuttles them into the brain using LRP receptors that are naturally expressed at the BBB.

• ANG1005, a conjugate of Angiopep-2 and paclitaxel, is the first new chemical entity to use this technology and the first drug candidate to be tested in humans to use a physiological approach to cross the BBB.

• Promising preclinical studies and preliminary clinical safety and tolerability data provide new hope to those dealing with brain cancers and, in future, possibly other brain diseases.