



# ATIII

## ANTITHROMBIN III

In 1999, Genzyme Transgenics made significant progress in the continued development of its lead product, recombinant human antithrombin III (ATIII). This product represents the most clinically advanced of any therapeutic product produced worldwide using transgenic technology. After completing Phase I and Phase II clinical studies, the Company initiated two identical, double blinded, randomized placebo-controlled Phase III clinical trials. These trials were designed to evaluate the safety and efficacy of ATIII in providing adequate anticoagulation in heparin-resistant patients undergoing elective cardiac surgery requiring cardiopulmonary bypass.

The first of these studies was conducted at six medical centers in Germany and the United Kingdom and was completed in 1999. Analysis of the data demonstrated that the primary endpoint of the study, reduction in the use of fresh frozen plasma, was successfully met, and that the results were statistically significant.

Of the 52 heparin-resistant patients enrolled in the Phase III study, the results demonstrated that only 21 percent, or 6 out of 28 patients, in the ATIII-treated group required fresh frozen plasma, compared to 92 percent, or 22 out of 24 patients, in the placebo group.

The trial also achieved statistical significance on two out of three secondary endpoints, including maintenance of normal ATIII levels during the bypass procedure and changes in D-dimer level, a biochemical marker of coagulation.

Patient enrollment in the second identically designed Phase III clinical trial, which is being conducted in the US and in Europe, is nearly complete. In 2000, Genzyme Transgenics looks forward to completing this second Phase III trial. Together with its partner, Genzyme General, the Company will focus on completing the necessary requirements and preparing documentation to support its anticipated regulatory filing around year-end. Key activities will include validation and documentation of the production and purification processes conducted at the Genzyme Transgenics farm and Genzyme facilities required to support the commercialization of ATIII, as well as presenting and publishing results of ATIII clinical trials.

ATIII is a protein normally found in human plasma which acts as an anticoagulant when bound to heparin and also has anti-inflammatory properties. Decreased levels of ATIII are found in individuals who have either a hereditary or an acquired deficiency of ATIII. In addition to heparin resistance, acquired ATIII deficiency can occur in multiple disease states, including sepsis, disseminated intravascular coagulation, liver disease, trauma, bone marrow transplantation and others.





The annual worldwide market for plasma-derived ATIII is approximately \$230 million.

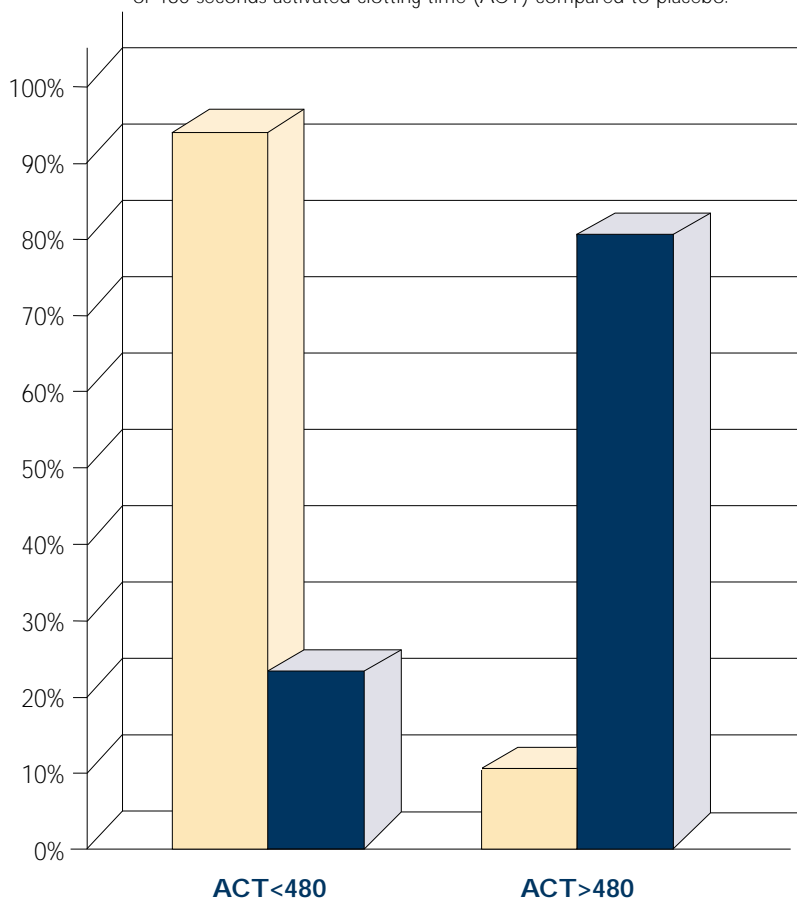
The Company is initiating collaborations with a number of academic researchers who are conducting preclinical studies to assess the potential medical use of ATIII in indications other than heparin resistance. These studies include investigating the role of ATIII in modulating immune responses and its effect on animal

models in conditions characterized by abnormal clotting such as sepsis and complications of bone marrow transplant. As an example, Dr. Judah Folkman at Children's Hospital in Boston reported in 1999 that a form of ATIII had potential application as an angiogenesis inhibitor in the field of oncology. This conformation of ATIII, referred to as antiangiogenic ATIII is in early research evaluation.

## PRIMARY EFFICACY ENDPOINT FOR PHASE III CLINICAL STUDY MET (P<.001)

### Primary Objective

To show that fewer patients receiving ATIII needed additional therapy (FFP) to reach anticoagulation goal of 480 seconds activated clotting time (ACT) compared to placebo.



### Trial Design

- 52 "heparin-resistant" subjects recruited from 6 sites (UK, Germany) did not have prolonged clotting times after 2 doses of heparin
- Randomized, double blinded, Phase III
- Placebo or ATIII administered after patients did not respond to heparin anticoagulation

Placebo  
ATIII

### Conclusion

Use of fresh frozen plasma (FFP) was significantly reduced in the heparin-resistant patients receiving ATIII compared to placebo.