

**Endocrinologic and Metabolic Drugs Advisory Committee
January 14, 2003**

Preliminary Discussion Topics

**Agalsidase alfa for the treatment of Fabry Disease
Transkaryotic Therapies, Inc.**

- 1) Study TKT-003 was designed with the primary objective of demonstrating a meaningful effect in the reduction of pain. Data were also collected on renal function and other clinical outcomes. The majority of the pain outcomes did not indicate a treatment-associated effect. Some aspects of study conduct (e.g., difficulties in definitions and recording of pain medication usage) also confound interpretation of the pain outcomes. Inconsistent and/or contradictory results on multiple renal function-related endpoints or cardiac-related endpoints prohibit reaching clear conclusions regarding beneficial effects of treatment on these organs. FDA determined that the data do not provide substantial evidence of treatment effect.

Please discuss the available clinical data, and any conclusions you are able to draw from these data regarding efficacy of the product.

- 2) In the controlled study TKT-003 tissue biopsies were collected and multiple histologic features analyzed as secondary or exploratory endpoints. These analyses were not prospectively planned in detail. The data indicate some effects on renal pathology, but the exact degree of treatment-associated change is unclear.

Please discuss the quality and strength of these data. Please include discussion of the importance of the renal endothelium cell type as compared to other renal cell types or tissues. Please discuss any conclusions you are able to draw from these data regarding efficacy of the product.

- 3) Data regarding endpoints other than clinical efficacy may, under some circumstances, be used as an unvalidated surrogate for efficacy. The accelerated approval regulations provide for marketing of a product based on such data.
- a) Please discuss the potential meaning of the histologic findings obtained by TKT.
 - b) Specifically, do you find that any or all of the histologic data are “reasonably likely to predict” clinical benefit, in the manner intended under the regulations for accelerated approval?
 - c) If not, do you recommend that any further evaluations of the existing biopsy samples be performed, with the possibility that these additional evaluations might be a suitable basis for an accelerated approval? If the answer is yes, then please discuss the types of re-analyses that would be most useful for TKT to perform.
- 4) Antibody formation against agalsidase alfa occurs in a substantial number of patients. There is the theoretical potential for these antibodies to impair the activity of the enzyme, either by direct neutralization or by altering the pharmacokinetics and cellular/organ distribution of enzyme uptake. Two year data in the open label extension study TKT-011 indicated that plasma levels of substrate (CTH) while still reduced compared to baseline were somewhat higher among subjects with persistently positive antibody by ELISA than among those who were not antibody positive or had been so only transiently. Urine sediment CTH content results may be consistent with also showing higher levels in subjects persistently antibody positive than those that are not.
- a) Please discuss your interpretation of these data. To what extent do these findings suggest a waning of enzyme activity.
 - b) In light of the need for long term, and likely life-long treatment, please discuss how important it is to obtain, and with what degree of rigor (e.g., degree of precision in ruling out a loss of activity) an evaluation of potential antibody-related loss of efficacy and/or activity.
 - c) If you view this as a critical requirement,
 - i) Is it reasonable to permit these data to be generated and evaluated after marketing approval, or should the data be available and integrated into a decision about marketing approval? Please bear in mind that rigorous assessment may be more difficult in the post-marketing situation.
 - ii) Please discuss the types of assessments and the time frame for assessment that you view as important to evaluation of this issue.