

## Endocrinologic and Metabolic Drugs Advisory Committee

### Questions to the Committee

January 14, 2003

#### **BL 103977 - Replagal™ (agalsidase alfa), Transkaryotic Therapies, Inc.** - proposed for the treatment of Fabry's disease.

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- 1) Data from two placebo-controlled clinical studies, TKT-003 and TKT-005, have been submitted to the license application. TKT has recently completed a third placebo-controlled clinical study, TKT-010.

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, cardiac function, and other clinical outcomes. The pain outcomes in Study TKT-003 did not indicate a treatment-associated effect. Study TKT-005 was designed with the primary objective of demonstrating a biochemical effect on GB3 content in heart biopsies. Data were also collected on renal and cardiac function outcomes. The study results did not demonstrate a treatment-associated effect on cardiac GB3 content.

While some renal function or renal histology outcomes suggested a treatment effect, they were secondary or exploratory endpoints in these studies, and were inconsistent and/or contradictory with multiple other endpoints. These data prohibit reaching clear conclusions regarding beneficial effects of treatment on these organs. FDA determined that the data do not provide substantial evidence of efficacy.

The primary endpoint of Study TKT-010 was evaluation of progression of renal impairment. While FDA has yet to receive the complete study report, TKT has stated that the results of this study do not provide statistically significant evidence of efficacy on progression of renal dysfunction.

Please discuss the available clinical data, and any conclusions you are able to draw from these data regarding efficacy of the product. Do you find that TKT has provided substantial evidence of efficacy of agalsidase alfa in the treatment of Fabry disease?

- 2) In the controlled study TKT-003 renal tissue biopsies were collected and multiple histologic features analyzed as secondary or exploratory endpoints. Only a portion of the analysis methods were prospectively planned in detail. The data suggest some effects on renal pathology, but the exact degree of treatment-associated change is unclear.

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 quality and strength of these data. Please discuss the potential predictive meaning of the histologic findings obtained by TKT. Please include discussion of the importance of the renal vascular endothelium cell type as compared to other renal cell types or tissues.

- b) Are any specific element(s) of the histologic data “reasonably likely to predict” clinical benefit, in the manner intended under the regulations for accelerated approval?
  - c) If you do not feel the histologic data at present are reasonably likely to predict clinical benefit, 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.
- 3) Fabry disease is a life-long disease, for which we do not presently have data on long term administration of agalsidase alfa. We have not observed clear clinical progression of the disease during the course of the clinical studies conducted to date. Antibodies against agalsidase alfa develop in a substantial number of patients. Antibody formation has the theoretical potential to limit the usefulness of the product, either by direct enzyme neutralization or by altering the pharmacokinetics and cellular/organ distribution of enzyme uptake. If this occurs, it is possible that administration of the enzyme early in the disease would result in antibody formation that eliminates any future potential clinical benefits. In this case, early administration of the enzyme to the asymptomatic or unimpaired patients might only serve to immunize the patients.

Two year data in the open label extension study TKT-011 indicated that plasma levels of substrate (GB3), while still reduced compared to baseline, were higher among subjects with persistently positive antibody by ELISA than among those who were never antibody positive or only transiently positive. Urine sediment GB3 content results trend towards higher levels in patients persistently antibody positive compared to those patients who do not have persistent antibody.

- 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 obtaining data assessing the long-term durability of efficacy or activity 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 evaluated prior to approving the product for marketing? Please bear in mind that controlled comparison assessment and particularly long-duration controlled comparison studies 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.
  - iii) Please discuss if data demonstrating an optimal time within the disease course at which to begin enzyme administration in order to provide clinical benefit is an alternative, or more or less preferable objective for product development.