

**Endocrinologic and Metabolic Drugs Advisory Committee
January 15, 2003**

**Preliminary Discussion Topics
Laronidase for Treatment of MPS-I
BioMarin, Inc.**

- 1) Study ALID-003 was a 6 month, randomized controlled study in 45 subjects. FVC was one of the two co-primary endpoints. The overall treatment-associated difference in percent-predicted FVC was a mean of 6 percentage-points, from a baseline of approximately 50% predicted. The p-value was 0.02 for this difference. The groups were different in FVC at baseline, 48 vs 54 %predicted (treated vs. control). This baseline difference was similar in magnitude to the treatment-associated outcome difference. Examination of the timecourse of FVC during the study indicates that much of this treatment difference was due to an immediate FVC decline only in the placebo group which did not progress during subsequent months, and a last evaluation improvement in the Laronidase treated group.

Please discuss the totality of the evidence regarding pulmonary function. Do the data support a meaningful Laronidase treatment effect on FVC?

- 2) Subset analyses of the FVC data suggest that, while a treatment-associated difference was observed for both male and female patients, the effect was different for each gender. Laronidase-treated females had improvements in FVC; placebo-treated females had a stable FVC. Laronidase-treated males had a stable FVC; placebo-treated males showed a decline in FVC.

Subset analyses also suggest that the treatment-associated outcome difference was more pronounced in patients who had the least amount of pulmonary impairment at baseline, with little difference between groups in the more advanced patients.

- a. Please discuss the exploratory analyses of FVC, and your interpretation of the data. If you have concluded (in #1) that laronidase has demonstrated a benefit on FVC, to which patient populations does this conclusion apply?
- b. Do these exploratory analyses raise enough concern to necessitate further investigation of subset-related interactions with treatment effect?
- c. If so, must this issue be clarified pre-marketing approval, or would post-approval exploration of the issue be suitable?

- 3) The distance walked in 6 minutes was the other co-primary endpoint. There was a 38 m difference between groups in the distance walked over the 6 minute period, from a baseline of more than 300 m in each group. The p-value for this difference was 0.07. The differences in 6 minute walk between groups at baseline was 319 vs 367 m in treatment and placebo groups, respectively. This baseline difference was more than the treatment-associated outcome difference. The net result was that by end of the randomized controlled portion of the study, the difference between groups present at baseline was largely absent.

Please discuss the evidence regarding walking distance. Do the data indicate that a meaningful treatment benefit has been demonstrated with laronidase treatment in walking capacity?

- 4) Exploratory analyses of the walking distance data showed that the treatment associated difference was entirely restricted to the female patients only. Baseline severity analyses did not suggest an interaction of severity with treatment, but analyses by age suggested that the overall treatment-associated difference was largely restricted to younger patients.
- a. Please discuss the exploratory analyses of walking distance, and your interpretation of the data. If you have concluded (in #3) that laronidase has demonstrated a benefit on walking capacity, to which patient populations does this conclusion apply?
 - b. Do you believe that these exploratory analyses raise enough concern to necessitate further investigation of subset-related interactions with treatment effect?
 - c. If so, must this issue be clarified pre-marketing approval, or would post-approval exploration of the issue be suitable?

- 5) Antibody formation was observed in nearly all laronidase treated subjects. This occurred early in the treatment course, usually within 2 months. Thus, 6-month findings on FVC and 6 minute walk were observed in the face of at least 4 months of antibody presence.
- a. Please discuss your degree of concern with the potential for antibodies against laronidase to diminish or eliminate longer-term efficacy.
 - b. Considering that this is a life-long disease requiring life-long treatment, please address to what extent data should be obtained on durability of effect.
 - c. Specifically, if additional clinical study data must be provided, please discuss the requisite nature of these data, such as the duration of observation and the necessity for (or absence of) controls.
- 6) The available clinical data suggest the major safety concerns for laronidase relate to infusion reactions. In general, the incidence of infusion reactions during the controlled study appeared similar between the two study groups. However, one placebo-treated patient in the controlled study subsequently received Laronidase in the extension study and experienced a life-threatening infusion reaction that required emergency tracheostomy. This subject had substantial respiratory impairment at baseline. The subject's serious adverse experience was temporally related to the Laronidase infusion and was cited as "definitely" related to Laronidase by the site investigator.

Please discuss the implications of this case in light of the potential use of Laronidase among subjects with profound respiratory impairment, including those with such profound impairment that they would not have qualified for enrollment into sponsor's major clinical studies.

- 7) Antibody formation was near universal in these subjects. Following marketing, Laronidase might be used among patients with residual, intrinsic iduronidase enzyme activity.

Please discuss any concerns you may have regarding the potential for antibody formation to worsen the clinical course in these patients.