FDA Summary of Controlled Clinical Data for Human IGF-1 in Treatment of Patients with Amyotrophic Lateral Sclerosis

FDA is aware of 5 sources of controlled clinical data evaluating recombinant human IGF-1 (rhIGF-1, or IGF-1) for treatment of patients with Amyotrophic Lateral Sclerosis (ALS or Lou Gehrig's disease). The data from these sources are summarized below.

The first 2 data sources are controlled clinical trials that were submitted by Cephalon in support of their New Drug Application (NDA) for the use of IGF-1 (proposed Tradename Myotrophin) in ALS. FDA has not approved IGF-1 for treatment of ALS.

Study 1200 (Neurology 1997;49:1621-1630)

Study 1200 was a multi-center clinical trial performed in the United States and Canada in which 266 patients with ALS were randomized to receive either IGF-1 0.05 mg/kg/day, IGF-1 0.1 mg/kg/day, or placebo, each given in a twice-daily regimen by subcutaneous injection. Patients were to be treated for 9 months, or until they reached one of 2 pre-specified endpoints: an Appel ALS Scale (AALS) score of 115, or a Forced Vital Capacity (FVC) of <39%. The Appel ALS Scale consists of 5 subscales (Bulbar Function, Respiratory Function, Overall Muscle Strength, Upper Extremity, and Lower Extremity Function) with scores ranging from 30 (Normal) to 164 (Maximal Dysfunction). Patients with a baseline AALS score of between 40 and 80 were eligible for inclusion in the trial. Approximately 90 patients were randomized to each treatment group.

The pre-specified primary outcome measure for the trial was a comparison of the rate of change (e.g., slope) of the total AALS score for the two IGF-1 groups combined compared to the slope for the placebo group, for patients who had at least 3 on-treatment AALS evaluations. For the primary outcome measure, there was no statistically significant difference between the combined IGF-1 groups and placebo. Secondary analyses of the trial showed a statistically significant difference in favor of the high-dose IGF-1 group compared to placebo. There was no statistically significant difference between the low-dose IGF-1 group and placebo.

Of the 30 patients who did not have 3 post-baseline AALS scores (about 10 patients per group) there were 3 deaths in each group. Of all randomized patients, 8%, 12%, and 9% of patients in the placebo, low dose, and high dose groups, respectively, died. This analysis included all data from patients, including data from patients after they met a pre-specified study endpoint (44 patients continued blinded treatment after having met a study endpoint). A total of 142 patients (53 on placebo, 44 on low dose, and 45 on high dose) met a study endpoint. Considering only the data from these patients up to the point of discontinuation (the protocol specified primary data set), there were 3, 4, and 7 deaths in the placebo, low dose, and high dose groups, respectively.

Study 1202 (Neurology 1998;51:583-586)

Study 1202 was a multi-center clinical trial performed in Europe using a protocol very similar to that used for Study 1200. Study 1202 differed from Study 1200 in the inclusion of only two treatment groups; 0.1 mg/kg/day IGF-1 and placebo, and the primary outcome measure was the total AALS score. The trial duration and pre-specified study endpoints were the same as in Study 1200.

A total of 124 patients were randomized to IGF-1, and 59 to placebo. There was no statistically

significant difference on the primary outcome measure between drug- and placebo-treated patients. A total of 15% of the drug-treated group, and 8% of the placebo-treated patients, died during double-blind treatment. According to the sponsor, there was an imbalance at baseline, with patients in the drug group having increased age and worse FVC, considered poor prognostic factors. By the sponsor's analyses, when these baseline imbalances were corrected for (in post hoc analyses), the difference in mortality was substantially diminished.

Mayo Clinic Study (Neurology 2008;71:1770-1775)

This was a multi-center clinical trial in which patients with ALS were randomized to receive IGF-1, 0.1 mg/kg/day or placebo given twice-daily for 2 years. There were a total of 330 patients at 20 centers in the United States. The primary outcome measure was the rate of change in the averaged manual muscle testing score (MMT). The MMT assesses strength in 34 muscle groups, and individual groups are scored on a 10 point scale. There was no statistically significant difference between treatment groups on the primary outcome, and no difference in mortality between the 2 groups.

Cephalon Treatment IND (unpublished data provided to FDA by the sponsor)

After the two controlled clinical trials of IGF-1 were completed (Studies 1200 and 1202 described above), Cephalon submitted a request for a Treatment IND (original request 10/10/95). The trial permitted patients who were 18 years old or older with a diagnosis of ALS to enter a lottery with the possibility of receiving IGF-1 0.1 mg/kg/day (given in a twice daily regimen). The sponsor proposed a lottery because they did not have sufficient supply of drug to make it available to all who wanted it. Those patients who entered the lottery and did not receive drug were continued to be followed in order to obtain mortality data in both the treated and untreated groups. For each patient who received drug, 10 were untreated. Over time, as additional drug was manufactured, a total of 10 lotteries were performed. Patients who did not receive drug at any given lottery were eligible to receive drug at a subsequent lottery.

The sponsor submitted data from the Treatment IND to the FDA on 8/14/98. The first lottery took place on 11/15/96, and the last lottery for which data were submitted took place on 8/13/97. Analysis of these data was complex and controversial, the controversy primarily related to how patients who did or did not receive drug were counted in the analysis. FDA statisticians expressed a concern that the time prior to a patient's selection to receive treatment with IGF-1 (if, of course, they were chosen) was considered to have been under treatment. That is, the total time of survival prior to receiving IGF-1 was considered survival under treatment with IGF-1, an obvious bias. Further, a patient who was not selected at any given lottery could be chosen in a subsequent lottery (assuming, of course, that the patient survived until that next lottery). A patient who did not get selected who died before the next lottery was considered unselected. This created a bias in the comparison between selected and unselected patients. FDA statisticians uncovered several other potential biases as well.

For these reasons, FDA statisticians recommended that the Agency focus its analysis on the results of the first 2 lotteries, which were felt to be least impacted by the potential biases noted above. FDA's analysis of the data from the first two lotteries found the following results:

Mortality in treated patients	Mortality in untreated patients	p-value
41/183 (22.4%)	262/1533 (17.1%)	0.14

The multiple analyses performed by FDA statisticians are shown in the table below:

Table 4. Survival analysis based on methods that minimize the bias

population	p-value	Risk ratio	95% CI
Non-parametric analysis			
The first two lottery patients	0.1357*	1.28	(0.92, 1.78)
The second lottery patients (1)	0.1320*	1.33	(0.92, 1.92)
The second lottery patients (2)	0.1708*	1.29	(0.89, 1.85)
The first five lottery patients	0.1495*	1.25	(0.92, 1.70)
Time dependent covariate (semi-parametric) analysis			
The first two lottery patients	0.3099**	1.22	(0.83, 1.80)
The first three lottery patients	0.1891**	1.29	(0.88, 1.88)
The first four lottery patients	0.1700**	1.29	(0.90, 1.86)
The first five lottery patients	0.1327**	1.32	(0.92, 1.89)
The fist six lottery patients	0.1305**	1.32	(0.92, 1.89)
All ten lottery patients	0.1526**	1.30	(0.91, 1.86)
All ten lottery patients /adjusted for age	0.0686**	1.40	(0.98, 2.00)

* log-rank test; ** Wald test; (1) survival days counted from the time of the second lottery; (2) survival days counted from the first eligible time

For all analyses of survival the risk ratio was >1.0, which favored placebo, however, none of the analyses achieved nominal statistical significance (i.e., $p<0.05$). A Kaplan-Meier curve of the survival data for the first two lotteries is provided in Attachment A.

Japanese Study (unpublished data submitted to FDA by Cephalon)

A study was performed in Japan by Kyowa Hakko, a partner of Cephalon. This was a randomized, placebo-controlled, parallel-group, clinical trial in which patients with ALS (AALS scores of 40-80 at screening) were randomized to receive IGF-1, 0.1 mg/kg/day (given twice daily) or placebo. The study duration was 9 months, and stopping rules were as in the Cephalon studies described above. FDA does not know what the pre-specified primary outcome measure was for this trial, but AALS score and "ALS Severity" were assessed, as well as "Overall Therapeutic Effects". There was an open label extension after patients completed the randomized portion of the trial, and based on an interim report of survival data, Kyowa Hakka apparently voluntarily discontinued treatment. The results of the mortality data for the controlled trial are given below:

IGF-1 Mortality	**Placebo Mortality**	**P-value**
47/78 (60.3%)	36/71 (50.7%)	0.14

An analysis of mortality that adjusted for baseline covariates yielded a p-value of 0.03, favoring placebo. A Kaplan-Meier Survival curve is provided in Attachment B.

Attachment A: Kaplan-Meier Survival Curve for First Two Lotteries from the Cephalon Treatment IND use of IGF-1 in patients with ALS

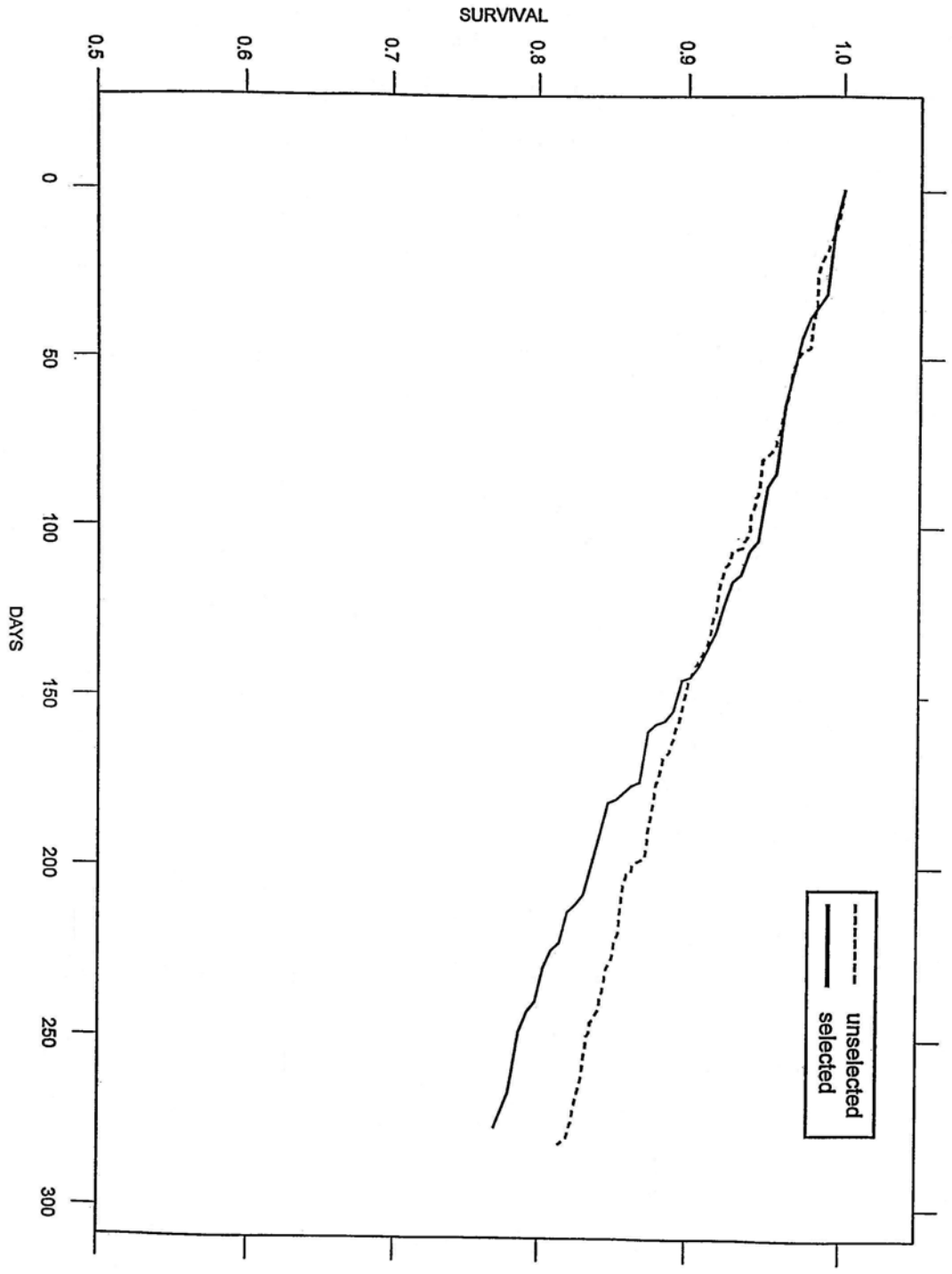
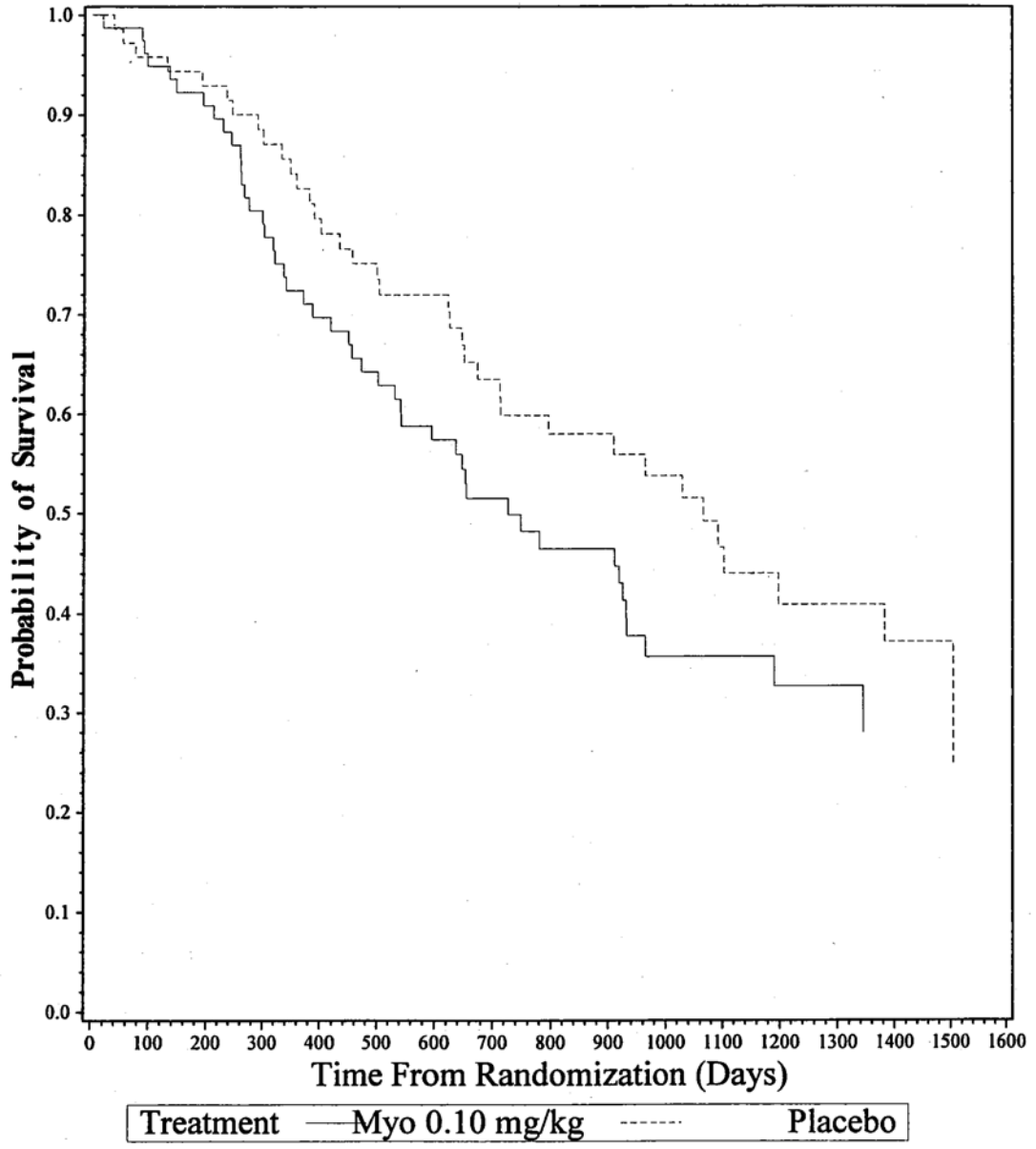


Fig. 1 Estimated survival curves / Lotteries #1 and #2

Attachment B: Kaplan-Meier Survival curve from Japanese trial of IGF-1 in patients with ALS

FIGURE 3

Kaplan Meier Survival Curve for Kyowa Hakko Study By Treatment Group



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