Growth Hormone and Intrahepatic Lipid Content in Patients with Nonalcoholic Fatty Liver Disease

NCT# 02217345

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Statistical Analysis Plan

A. Study endpoints

Primary Endpoint: Change in intrahepatic lipid accumulation over 6 months in the GH vs placebo group.

Secondary Endpoints: Change in the following endpoints over 6 months in the GH vs placebo group.

1. Liver function tests
2. Adipokines: leptin and adiponectin
3. Inflammatory markers: hsCRP, IL-6 and TNF alpha receptors
4. Measures of insulin resistance
5. Abdominal fat compartments
6. NAFLD Fibrosis Score
7. ELF Score
8. Liver stiffness by Fibroscan
9. Liver inflammation and fibrosis by Liver *MultiScan*

B. Experimental approach:
A total of approximately 65 otherwise healthy subjects with NAFLD and relatively low IGF-1 levels will be enrolled after a screening visit at which study eligibility will be determined with a history, physical exam, blood work, IGF-1 level and hemoglobin A1C. Eligible subjects will be randomized to receive GH or placebo. GH reserve will be characterized at baseline. Subjects will be studied for 6 months. We plan to enroll up to 65 individuals and will attempt to replace subjects who have dropped out of the study to ensure 50 completers at 6 months.

C. Statistical power and Analysis
Power Calculation: A total of approximately 65 patients will enter this two-treatment parallel-design study with enrollment of up to 50 completers. With 40 completers, the probability is increased to 90 percent that the study will detect a treatment difference in percent intrahepatic lipid content at a two-sided 0.05 significance level, if the true difference between treatment with GH and placebo is 6.5%. With 50 completers, the probability is 90 percent that the study will detect a treatment difference in percent intrahepatic lipid content at a two-sided 0.05 significance level, if the true difference between treatment with GH and placebo is 5.7%. This is based on the assumption that the standard deviation of the response variable is 6.1% as observed in Wong *et. al*.[1] Studies available for power calculations include all comers with NAFLD, and our study population is restricted to those without diabetes who are more likely to have a lower severity of disease. Additionally, there is recognized variability in the natural history of NAFLD, particularly in early stage disease. For these reasons, we will attempt to replace subjects who have dropped out of the study to ensure 50 completers at 6 months.

Data Analysis Plan: We will pool data from men and women using a random slopes model; we will consider a model where each study subject has a random slope and intercept. The primary analysis is a pooled analysis of treatment effect across gender with weights equaling the frequency of men and women in the sample. A secondary analysis will test for the significance of the treatment-gender interaction on the rate of change of intrahepatic liver fat and all other endpoints. For all analyses, an intent-to-treat analysis will be performed.

(1) Wong VW, Chan RS, Wong GL, Cheung BH, Chu WC, Yeung DK, Chim AM, Lai JW, Li LS, Sea MM, Chan FK, Sung JJ, Woo J, Chan HL. Community-based lifestyle modification programme for non-alcoholic fatty liver disease: a randomized controlled trial. *Journal of hepatology*. 2013;59(3):536-542.