A Phase IIb study to Evaluate the Safety, Tolerability, Pharmacokinetic and Pharmacodynamic Profile of ARX201 Following Repeated Dosing to Young Adult Patients with Childhood Onset Growth Hormone Deficiency

Sponsor:	Ambrx, Inc.
Coordinating Investigator	Prof. Karoly RÁCZ, MD PhD
Sponsor's Medical Officer	Douglas W. Axelrod, MD PhD
Study/Protocol No.:	PRO-ARX201-701
Study Medication Name:	ARX201 (a modified human recombinant growth hormone conjugated to a 30,000 Dalton linear poly(ethylene) glycol)
Development Phase:	Phase IIb
Indication:	Childhood Onset Growth Hormone Deficiency
Date of First Enrollment:	28-Oct- 2008
Date Last Patient Completed:	24-Sep-2009
Date of Report:	03-June-2010, Final

The study was conducted according to the protocol and in compliance with Good Clinical Practice (GCP) and other applicable regulatory requirements.

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2. CLINICAL STUDY SYNOPSIS

Name of Company: Ambrx, Inc. **Name of Finished Product:** ARX201 **Name of Active Ingredient(s):** pegylated human recombinant growth hormone	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For national authority use only)**
Title of Study: A Phase IIb study to Evaluate the Safety, Tolerability, Pharmacokinetic and Pharmacodynamic Profile of ARX201 Following Repeated Dosing to Young Adult Patients with Childhood Onset Growth Hormone Deficiency (GHD)		
Protocol Number: PRO-ARX201-701		
Study Period: **Date of first enrollment:** 28Oct2008 **Date last patient completed:** 24Sep2009		
Phase of Development: Phase IIb		

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Publication(s): None

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Objectives: The primary objective of this study was to evaluate the safety, tolerability, and pharmacodynamic (PD) response of three different ARX201 doses when administered as repeated doses to young adult patients with childhood onset GHD.		
Study Design: Multicenter, 26-week, randomized, open-label study of 3 doses of ARX201 administered weekly. Male patients had 4 weeks of post-treatment follow-up, and female patients had 12 months of post-treatment safety follow-up, the latter to be described in a supplemental report.		
Number of Patients (planned and analyzed): A total of 40-45 patients were planned, with at least 12 patients completing each Cohort. A total of 89 patients were screened, 44 patients were randomized, 43 patients received study treatment, and 27 patients completed the study. Among the 16 patients not completing the study treatment, 11 female patients were removed by the Sponsor in accordance with a protocol amendment and 5 patients discontinued due to withdrawal of consent or non-compliance.		
Diagnosis and Main Criteria for Inclusion: Men and women aged 18 to 30 years with growth hormone deficiency of childhood onset. Growth hormone (GH) levels below the predetermined cut-off value in one of the dynamic endocrine tests (insulin tolerance, arginine-growth hormone releasing hormone (GHRH) or arginine test) or at least three other pituitary hormone deficiencies. Baseline insulin-like growth factor- 1(IGF-I) level of $\leq$ -2 standard deviation score (SDS) standardized for age and sex according to the central laboratory reference values.		
Test Product, Dose and Mode of Administration, and Lot Number(s): The active component of the product ARX201 is a modified human growth hormone (hGH) conjugated to a 30,000 Dalton linear poly(ethylene) glycol. The unconjugated biosynthetic product of host *E. coli* comprises a 191 amino acid protein with biophysical stability, activity and potency properties comparable to native hGH. ARX201 was supplied in a single-use 3 mL clear glass vial with a gray fluortec stopper and blue flip-off overseal; each vial contained 14.5 mg of ARX201 drug substance as a sterile, nonpyrogenic, white, lyophilized powder administered subcutaneously (sc), once weekly for a period of 26 weeks. Batch number: CMC-B-0045/CT0730.		
Reference Therapy, Dose and Mode of Administration, and Lot Number(s): Not applicable		
Duration of Treatment: 26 weeks		

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Criteria for Evaluation:

Primary efficacy endpoint

- Temporal profiling of circulating IGF-I levels

Secondary efficacy endpoints

- IGF-I SDS; changes from baseline in IGF-I level, IGF-I SDS;
- IGFBP-3, IGFBP-3 SDS (actual values and changes from baseline)
- Lipid parameters (Cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides; actual values and changes from baseline)

Clinical endpoints

a) Change in body fat mass (FM) from baseline, as measured with dual-energy x-ray absorbtiometry (DXA)
b) Relative change in body fat
c) Change in trunk fat
d) Relative change in trunk fat
e) Change in lean body mass (LBM) from baseline, as measured with DXA
f) Change in waist circumference
g) Change in hip circumference
h) Change in waist-to-hip ratio
i) Change in sum of skinfold thickness
j) Change in body mass index (BMI)
k) Change in quality of life (QoL) scores

Safety

Adverse events (AEs), parameters of glucose metabolism (fasting insulin level, fasting glucose level, HbA1c levels), immunogenicity (Anti-ARX201 antibody occurrence), IGF-I levels, status of other hormonal axes: thyroid hormones (free T4, T3 and thyroid stimulating hormone (TSH)), cortisol and prolactin levels, other safety laboratory parameters, including serum chemistry profile, liver enzymes, hematology, and urinalysis, electrocardiography (ECG), echocardiography results, local tolerability (i.e., injection site reaction), physical examination and fundoscopy.

Pharmacokinetic Assessments: Blood samples for analysis of serum concentrations were collected prior to dosing with the investigational product and with intensive pharmacokinetic (PK) profiling during the 1st, 14th and 26th week of treatment with appropriate intermediate timepoints for a complete assessment of PK and PD.

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Statistical Methods:

Analysis Subsets (populations):

- Safety analysis Subset: All patients who have received at least one dose of active treatment.
- Full analysis Subset (FAS): All randomized patients who have received at least one dose of active treatment and who provided any follow-up data for the primary target variables.
- Per protocol Subset (PP): Patients without major protocol deviations or premature termination of treatment due to reasons that were definitely not related to study medication.

Efficacy: All summaries of efficacy variables are stratified by Cohort. The analyses are descriptive and exploratory based upon descriptive summary statistics. Statistical comparisons between each ARX201 dose level was performed for the main efficacy endpoint using an analysis of covariance (ANCOVA) model. The independent variables in the model included the baseline IGF-I value as a covariate and treatment as a fixed effect (2.5, 5 and 10 mg of ARX201). Differences among treatment group least squares means were tested for significance, and p-values for these comparisons reported without any adjustment for multiplicity. Normal distribution of secondary efficacy parameters was evaluated in linear scale; if not normally distributed, logarithmical transformation was performed. In case normal distribution of data was reached, analysis of variance (ANOVA) was used. Otherwise, a non-parametrical Wilcoxon test was used. All statistical tests were two-sided, and the level of significance alpha = 0.05. Confidence intervals were calculated at a 95% confidence level.

Safety: Analyses are descriptive and based upon descriptive summary statistics.

Pharmacokinetics: Serum ARX201 concentrations were plotted against time for each patient. Pharmacokinetics parameters were calculated for all patients, as appropriate to Periods I and II, using WinNonlin Enterprise Float (Version 5.2.1).

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Safety Results: A total of 55 TEAEs were reported by 17 out of 43 patients. The most commonly reported events were peripheral edema, edema, decreased FT4, nasopharyngitis, and pharynoglaryngeal pain; each of these events occurring in 3 (7%) patients. There were no severe AEs and one unrelated SAE. The most common possibly or probably related AEs were edema and peripheral edema. However, there was variability in dose response as certain patients exhibited GH related AEs at 2.5 mg while others tolerated 10 mg well. Neutralizing antibodies occurred transiently in low titer in one patient; these antibodies dissipated with continued therapy. Having started with IGF-I levels substantially lower than the cohort's distribution, this patient's IGF-I levels entered the cohort's IGF-I distribution by week 15. In general, insulin levels rose slightly, peaking at 48h post dose. However, glucose homeostasis was not adversely affected in the long term, as documented with normal HbA1c levels, demonstrating patient tolerance to weekly dosing of ARX201 at levels capable of normalizing IGF-I values. No significant concerns were identified for local tolerability, vital signs, physical examinations, ECG, echocardiography or fundoscopy.

Efficacy Results: Analyses of total and LDL cholesterol, triglycerides, body composition, and quality of life showed favorable responses in all Cohorts. Statistically-significant differences in IGF-I were observed in a comparison of Cohorts 2 and 3 vs Cohort 1 and in lean body mass in comparison of Cohort 3 vs Cohort 1 (these analyses were performed on PPR Subset). Minimum, maximum and mean IGF-I were significantly changed with respect to baseline. Changes did not reach statistical significance for serum lipid and fat mass parameters, however lean body mass was significantly increased in Cohort 3 and overall. The trial was not powered to prove efficacy, and the efficacy analyses were planned to be descriptive only.

Pharmacokinetics Results: The long T_{max} of ARX201 is in contrast to observed values after subcutaneous administration of marketed non-pegylated GH preparations in GH deficient adults. There was a trend towards higher T_{max} at Weeks 14 and 26 with respect to Week 1. There was also greater than dose-proportional increase in exposure to ARX201 at Weeks 14 and 26. Trough concentrations at 7 days post dose increased at later visits compared to the first post-dose trough value. The accumulation remained stable without apparent further increases during the study, yet sufficient to ensure sustained effect.

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Conclusions: Overall, the results of trial PRO-ARX201-701 indicate that all three investigated doses were safe and well-tolerated. A single patient's demonstration of immunogenicity supports the need for continued monitoring in future clinical trials. Positive PD and selected elements of positive efficacy were also demonstrated in all Cohorts.		
Date of Report: 03-June-2010		