# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-538**

## OTHER REVIEW(S)

**M E M O R A N D U M**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**PUBLIC HEALTH SERVICE**
**FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**

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# CLINICAL INSPECTION SUMMARY

DATE: January 18, 2007

TO: Kati Johnson, Chief, Project Management Staff
Dragos Roman, M.D., Clinical Reviewer
Division of Metabolism and Endocrinology Products

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

FROM: Andrea Slavin, RN
Consumer Safety Officer

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-538

APPLICANT: Cangene Corporation

DRUG: Accretropin™ [somatropin (rDNA origin)] injection

THERAPEUTIC CLASSIFICATION: 5, S

INDICATIONS: Treatment of pediatric patients who have growth failure due to an inadequate secretion of normal endogenous growth hormone.

Treatment of short stature associated with Turner's Syndrome in pediatric patients whose epiphyses are not closed.

CONSULTATION REQUEST DATE: June 22, 2006

DIVISION ACTION GOAL DATE: March 9, 2007

PDUFA DATE: March 10, 2007

## I. BACKGROUND:

Accretropin™ is recombinant human growth hormone, which has been shown to be chemically and biologically equivalent to pituitary-derived human growth hormone. It is not a new molecular entity.

The goals of the inspections were to assess adherence to FDA regulatory requirements, specifically, investigator oversight, protocol compliance, verification of primary efficacy endpoint data (heights), adequacy of study records and protection of subjects' rights, safety, and welfare.

In addition, the inspection focused on the procedures used by the site to obtain height measurements and vital signs. The site for studies GA-005/5A was selected based on the number of subjects enrolled. There was only one site for studies GA-007/7A.

The following studies were audited:

#GA-005, "Recombinant Human Growth Hormone (r-hGH) for the Treatment of Children with Growth Hormone Deficiency"

#GA-005A, "Recombinant Human Growth Hormone (r-hGH) for the Treatment of Children with Growth Hormone Deficiency – Long-Term Follow-Up Trial"

#GA-007, "Recombinant Human Growth Hormone (r-hGH) for the Treatment of Children with Turner's Syndrome"

#GA-007A, "Recombinant Human Growth Hormone (r-hGH) for the Treatment of Children with Turner's Syndrome – Long-Term Follow-Up Trial"

Summary Report of Inspections

II. RESULTS (by protocol/site):

| Name of CI and site #, if known | City | Country | Protocols | Inspection Date | EIR Received Date | Final Classification |
|---|---|---|---|---|---|---|
| Prof. Tomasz Romer<br>Dr. Miecczyslaw Walczak | Warsaw | Poland | GA-005/5A<br>GA-007/7A | 8/21/06-9/1/06 | 10/3/2006 | VAI |

Dr. Mieczyslaw Walczak assumed investigator responsibilities when Dr. Romer retired.

Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.
VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability
OAI = Significant deviations from regulations. Data unreliable.

A. Protocols #GA-005/5A

Prof. Tomasz E. Romer/Dr. Mieczyslaw Walczak (site 100)
Instytut Pomnik Centrum Zdrowia Dziecka
Klinika Endokrynologii
Aleja Dzieci Polskich 20
04-736 Warsaw, Poland

a. What was inspected: At this site, 24 subjects were screened and enrolled into study 005. Twenty-two subjects completed the study and were enrolled in the follow-up study, 005A. Fourteen subjects completed 005A. All subjects' records were audited for informed consent and height measurements. Six subjects' records were audited for data integrity.

b. Limitations of inspection: Study records are in the Polish language. Translators were used as needed.

c. General observations/commentary: Subject 124 did not meet the inclusion criterion of child bone age radiograph being 30% or less of chronological age; for subject 111, serious adverse event (SAE) of pneumonia/chickenpox was not reported to the sponsor within the protocol-required time frame. Drug accountability forms had design limitations and numerous corrections, which made it difficult to reconcile the amount of study drug received by the site, dispensed, and returned by subjects. Also, calculations performed by the site to determine eligibility (stature of < -2 SDS for chronological age and < -1 SDS for growth velocity, child bone age) were collected by the sponsor and were not maintained at the site.

d. Data appear acceptable.

B. Protocols #GA-007/7A

Prof. Tomasz E. Romer/Dr. Miecyslaw Walczak
Instytut Pomnik Centrum Zdrowia Dziecka
Klinika Endokrynologii
Aleja Dzieci Polskich 20
04-736 Warsaw, Poland

a. What was inspected: Thirty-seven subjects were screened and enrolled into study 007. All subjects completed the study and were enrolled in the follow-up study, 007A. Thirty-six subjects completed 007A. All subjects' records were audited for informed consent and height measurements. Nine subjects' records were audited for data integrity.

b. Limitations of Inspection: Study records are in the Polish language. Translators were used as needed.

c. General observations/commentary: Subject 501 received an incorrect dose (0.08 mg/kg/day) from the month 12 to the month 18 visit; for subject 520, SAE of lymphadenitis was not reported to the sponsor within the protocol-required time frame; subject 522 did not meet the inclusion criterion for age (subject was 7.8 years old); AEs of nephritis (subject 536) and mild scoliosis (subject 523) were not listed in the sponsor's data listing. Also, calculations performed by the site to determine eligibility (stature of < -2 SDS for chronological age and < -1 SDS for growth velocity, child bone age) were collected by the sponsor and were not maintained at the site.

d. Data appear acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

As stated above, subject 124 did not meet inclusion criteria for study GA-005 and subject 522 did not meet inclusion criteria for study GA-007. Overall, data appear acceptable.

*{See appended electronic signature page}*

Andrea Slavin, RN
Consumer Safety Officer

CONCURRENCE:

*{See appended electronic signature page}*

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

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/s/
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Andrea Slavin
1/24/2007 09:08:36 AM
CSO

Constance Lewin
1/24/2007 10:45:05 AM
MEDICAL OFFICER