CLINICAL STUDY REPORT

An Open-label, Multi-centre, Phase III Study of Local Tolerability of ZOMACTON 10 mg (Recombinant Somatropin) administered by ZomaJet Vision X

Children with growth failure due to inadequate secretion of growth hormone or growth retardation due to Turner's syndrome are individually dosed and treated for 12 weeks

FE999905 CS002

EudraCT number:	2005-001539-31
IND number:	Not applicable
Investigational product:	ZOMACTON 10 mg administered by ZomaJet Vision X. Powder and solvent for solution. Subcutaneous administration by use of ZomaJet Vision X
Indication:	Long-term treatment of children who have growth failure due to inadequate secretion of growth hormone and for the long-term treatment of growth retardation due to Turner's syndrome confirmed by chromosome analysis
Phase:	III
Name and address of Sponsor:	Ferring Pharmaceuticals A/S PharmaScience Center Kay Fiskers Plads 11 2300 Copenhagen S Denmark Tel. (+45) 8833 8834
GCP statement:	This study has been performed in compliance with GCP.

SYNOPSIS

TITLE OF STUDY: An Open-label, Multi-centre, Phase III Study of Local Tolerability of ZOMACTON 10 mg (Recombinant Somatropin) administered by ZomaJet Vision X.

CO-ORDINATING INVESTIGATOR: [redacted]

CENTRAL ASSESSOR: [redacted]

STUDY CENTRE(S):

The study was conducted 6 centres in 3 countries: the Netherlands (1), France (2) and Czech Republic (3).
The main study centre was: [redacted]

The central assessor was based at: [redacted]

PUBLICATION (REFERENCE): Not applicable.

STUDIED PERIOD (YEARS):	**PHASE OF DEVELOPMENT:**
10 October 2005 30 March 2006	III

OBJECTIVES:

Ferring Pharmaceuticals A/S has developed a new ZOMACTON 10 mg formulation. The formulation provides a higher concentration and thereby a smaller volume to be administered. ZomaJet Vision X is a needle-free injection system. It sends a thin jet of ZOMACTON through the skin and into the subcutaneous tissue without the use of a needle. The mode of administration is referred to as "transjection". By use of ZomaJet Vision X, both transjection and reconstitution of ZOMACTON 10 mg can be done without using a needle. The rationale of the study was to describe the local tolerability of the new ZOMACTON 10 mg administered by ZomaJet Vision X.

Primary objective

- To assess the local tolerability of an individualised dose of ZOMACTON 10 mg administered by ZomaJet Vision X.

Secondary objectives

- To assess the frequency of local tolerability reactions when administering an individualised dose of ZOMACTON 10 mg by ZomaJet Vision X by local assessor.
- To assess the frequency of local tolerability reactions when administering an individualised dose of ZOMACTON 10 mg by ZomaJet Vision X by central assessor.
- To assess the frequency of immediate local reactions after administration of an individualised dose of ZOMACTON 10 mg by ZomaJet Vision X.
- To assess the subject's evaluation of pain associated with transjection of an individualised dose of ZOMACTON 10 mg administered by ZomaJet Vision X.
- To assess the subject's evaluation of itching associated with transjection of an individualised dose of ZOMACTON 10 mg administered by ZomaJet Vision X.

METHODOLOGY:

This was a prospective open-label study in subjects with growth failure due to inadequate secretion of growth hormone or growth retardation due to Turner's syndrome. The subjects received 12 weeks treatment with individualised doses of ZOMACTON 10 mg administered by ZomaJet Vision X.
The observation of area used for transjection by the pre-defined clinical terms provided a standardised description of findings. The central dermatologist assessment secured a uniform description. The study was designed to increase the likelihood of recording local acute reactions by injecting on one side only.

The considerable total number of transjections administered by subjects in the study supported the likelihood of observing local tolerability reactions usually only seen rarely. Local tolerability reactions experienced during a treatment period of 12 weeks were considered adequate to reflect local tolerability reactions seen during long-term treatment.
Transjections were to be done on one side of the body, opposite to the side of the body used for administering growth hormone prior to entering the study. If the subject used both sides prior to study entry, one side was to be chosen by the investigator by use of best clinical judgement.
Visits to the clinic took place at screening/treatment initiation (V_0), after 2 weeks (V_2), 6 weeks (V_6), and 12 weeks (V_{12}), of treatment. At each visit, the investigator assessed local tolerability reactions in the area used for transjections. Photos of the area used for transjections were taken for central assessment by a dermatologist. At each visit all reactions were counted, potentially including any reactions that were counted at the prior visits. Thus at each visit the accumulated occurrences were counted. At Visits V_0, V_2 and V_6, the daily transjection was done at the clinic. The investigator assessed immediate local reactions and the subject assessed the pain and itching associated with the transjection. Following V_0, visits to the clinic for proper instruction in use of ZomaJet Vision X were offered as needed. At Visits V_2, V_6 and V_{12}, subjects were asked to report any unusual transjection-related experiences occurring in the week prior to the visit.
The first protocol amendment clarified the text relating to pregnancy testing, reporting of transjection-related adverse events (AEs), withdrawal criteria and contraception for centres in France and the Netherlands. An adapted version of this amendment was approved for the 3 study centres in the Czech Republic (clarifying the text relating to pregnancy testing, reporting of transjection-related AEs and withdrawal criteria).
Protocol amendment 2 was implemented as a result of a request from the Ethics Committee in the Netherlands and provided an option for extension of the study at one centre in the Netherlands, with the purpose of compassionate use for 24 weeks after the study had ended. Only AEs, change in concomitant medication, local reactions normally recorded by the investigator outside of a study and drug administration were to be recorded.

NUMBER OF SUBJECTS:

It was planned that a minimum of 24 subjects would enter the study.
Twenty-seven subjects entered the study and were dosed. Twenty-six subjects completed the study.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Subjects between the ages of 3 and 17 years (both inclusive) with growth failure due to inadequate secretion of growth hormone or growth retardation due to Turner's syndrome. Subjects were to have been receiving growth hormone therapy for a minimum of 6 months prior to study enrolment.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:

ZOMACTON 10 mg was provided by Ferring Pharmaceuticals A/S as a vial with lyophilized powder and a pre-filled syringe with solvent (1 mL) for solution for transjection (batch number 51710). All subjects received the same batch.
ZOMACTON 10 mg was administered by the needle-free device ZomaJet Vision X. This is similar to the ZomaJet Vision 2 device already on the market for use with ZOMACTON 4 mg, the only differences being the scale and the name engraved on the device. ZomaJet Vision X provides a subcutaneous (s.c.) administration of the product. The dose of ZOMACTON 10 mg for each subject was according to the diagnosis made.
Growth Hormone Deficiency:
Generally a dose of 0.17 - 0.23 mg/kg body weight per week divided into 6 - 7 s.c. injections is recommended (corresponding to a daily injection of 0.02 - 0.03 mg/kg body weight).
Turner's Syndrome:
Generally a dose of 0.33 mg/kg body weight per week divided into 6 - 7 s.c. injections is recommended (corresponding to a daily injection of 0.05 mg/kg body weight).
The investigator could adjust the dose of ZOMACTON 10 mg in accordance with local practice at any time during the study in order to optimise the treatment of the subject.

DURATION OF TREATMENT:

Subjects were treated with individualised doses of ZOMACTON 10 mg for a period of 12 weeks in the study.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:

Since the study was non-comparative, no reference therapy was administered.

CRITERIA FOR EVALUATION:

Primary endpoint

- The proportion of subjects discontinuing after treatment start due to unacceptable transjection-related local tolerability reactions when receiving an individualised dose of ZOMACTON 10 mg administered by ZomaJet Vision X.

Secondary endpoints

Area used for transjections

- Assessed by local assessor: The occurrence of transjection-related punctual haemorrhage, transjection-related bruising, transjection-related inflammation - diffuse, transjection-related inflammation - nodular, transjection-related change in pigmentation, transjection-related dermal atrophy, transjection-related lipo-dystrophy and transjection-related sclerosis or scar formation when administering an individualised dose of ZOMACTON 10 mg by ZomaJet Vision X.
- Assessed by central assessor by use of photo of dermal area used for transjections: The occurrence of transjection-related punctual haemorrhage, transjection-related bruising, transjection-related inflammation - diffuse, transjection-related inflammation - nodular, transjection-related change in pigmentation, transjection-related dermal atrophy, transjection-related lipo-dystrophy and transjection-related sclerosis or scar formation when administering an individualised dose of ZOMACTON 10 mg by ZomaJet Vision X.

The presence/absence of each condition was indicated by number of occurrences. Occurrences were graded: mild, moderate, severe.

Immediate local reactions

- Assessed by subject: Impression of transjection-related pain and transjection-related itching when administering an individualised dose of ZOMACTON 10 mg by ZomaJet Vision X. Assessments were made within 10 minutes after administration.
- Assessed by local assessor: The occurrence of transjection-related punctual haemorrhage, transjection-related redness, transjection-related diffuse dermal swelling when administering an individualised dose of ZOMACTON 10 mg by ZomaJet Vision X. Assessments were made 15 and 60 minutes after administration. The absence/presence of occurrences was graded: none, mild, moderate, severe.

Safety Endpoints

- Frequency and severity of AEs.

STATISTICAL METHODS:

Statistical methods

The proportion of subjects where the primary reason for withdrawal was recorded as unacceptable transjection-related local tolerability reactions was calculated and the 95% confidence interval (CI) reported.

The proportion of transjection-related local tolerability reactions assessed by the local assessor (punctual haemorrhage, bruising, inflammation - diffuse, inflammation - nodular, change in pigmentation, dermal atrophy, lipo-dystrophy and sclerosis or scar formation) was tabulated by visit. In addition, the number (count) of each of these clinical observations per subject was summarised by descriptive statistics in total and by severity. The evaluations performed by the central assessor were summarised in the same way. The subject's impressions of transjection-related pain and itching were summarised by descriptive statistics.

The immediate local reactions of transjection-related punctual haemorrhage, redness and diffuse dermal swelling were summarised as described above for the local/central assessments by time point relative to administration. Treatment emergent AEs were summarised.
It was initially planned to perform analysis on the tolerability data using the intention-to-treat (ITT) dataset only. As a result of a major protocol deviation at one centre where subjects administered transjections to both sides of the body, a per-protocol (PP) dataset and an injection site switchers (ISS) dataset were defined to assess the potential impact of the violation on the results. These datasets were defined before database lock.

TOLERABILITY RESULTS:

One subject out of 27 was withdrawn as a result of an unacceptable transjection-related local tolerability reaction. The proportion (95% CI) was 0.037 (0.001, 0.190).
There was a cumulative increase at each visit in the frequency of transjection-related local tolerability reactions in both the local and central assessment. Punctual haemorrhage and bruising were the most frequent transjection related local tolerability reactions in both the local and central assessments. Change in pigmentation was the next most frequent reaction in the local assessment, but this reaction was not recorded for any subject by the central assessor.
The majority of transjection-related local tolerability reactions were classified as mild in severity by the local investigators and by the central assessor. One instance of bruising was classified as severe by the local investigator, however the maximum severity of bruising reported by the central assessor was moderate.
In the assessment of immediate tolerability reactions (i.e. reactions occurring in the 60 minutes after dosing), punctual haemorrhage and redness were more frequent than diffuse dermal swelling. In general, the incidence of punctual haemorrhage was greatest at 0 minutes and decreased at 15 and 60 minutes after the transjection. The incidence of redness and diffuse dermal swelling was greatest at 15 minutes after the transjection. The majority of immediate local tolerability reactions were classified as mild by the investigator.
The results of the subject assessment of pain and itching showed ZOMACTON 10 mg administered by ZomaJet Vision X was well tolerated in the majority of subjects. The proportion of subjects experiencing no pain increased by visit. Only one subject reported transjection-related itching during the study at one visit.
The analysis comparing the PP and ISS datasets indicated that the results obtained in the ITT population are unlikely to have been significantly affected by the major protocol violation.

EXPOSURE RESULTS:

The mean (SD) number of transjections received was 78.6 (14.6), the median was 83.0 and the range was 13 (Subject 0201-002 who was withdrawn from the study at V_2) to 91 transjections. The mean (SD) total dose received was 95.30 (52.84) mg, the median was 73.00 mg with a range of 24.7 to 224.0 mg.
Actual doses of ZOMACTON 10 mg given in the study ranged from 0.010 to 0.050 mg/kg body weight daily.
At the end of the study, all 6 subjects at the centre in the Netherlands chose to continue treatment with ZOMACTON 10 mg, as allowed for under the option of compassionate use.

SAFETY RESULTS:

There were no deaths during the study and no serious AEs or severe AEs were reported. One subject had an AE leading to withdrawal of the study drug (application site pain). This AE was considered by the investigator to be of moderate intensity and probably related to the investigational medicinal product. The subject was withdrawn from the study after discussion with the family, with the reason for withdrawal given as unacceptable transjection-related local tolerability reaction. Only two other AEs were reported during the study; both influenza of mild intensity, neither of which was considered to be related to the study drug.
There were no notable mean changes during the study in body weight, height or body mass index and no clinically significant vital signs values.

RESULTS:

One subject out of 27 (proportion 0.037, 95% CI: 0.001, 0.190 in the ITT dataset) was withdrawn as a result of an unacceptable transjection-related local tolerability reaction.

The most frequent local tolerability reactions recorded by the local assessor were punctual haemorrhage and bruising, followed by change in pigmentation.

The most frequent local tolerability reactions recorded by the central assessor were punctual haemorrhage and bruising. The central assessor did not record any instances of change in pigmentation. The incidence of the total number of local tolerability reactions increased cumulatively by visit. This may partly be explained by the fact that at each visit all reactions were counted, potentially including any reactions that were counted at the previous visits.

The majority of local tolerability reactions were classified as mild in severity by the local and central assessors. Only one reaction (bruising in one subject) was classified as severe by the local investigator, however the maximum severity of bruising reported by the central assessor was moderate.

Punctual haemorrhage occurred most frequently at 0 minutes and decreased at 15 and 60 minutes after transjection. Redness and diffuse dermal swelling occurred most frequently at 15 minutes after transjection. This was considered to reflect the normal skin physiology following an injection. The majority of immediate local reactions were classified as mild by the investigator.

The study included, due to the accumulative design of counting all reactions at each visit, a large number of observations with an observation period up to 12 weeks. This time frame was considered to be of sufficient length to allow for detection of potential long term transjection site adverse reactions. The study provided no evidence of local long-term effects or unexpected intolerance events.

The procedure was well accepted by the subjects in terms of pain and itching on transjection. The incidence of pain decreased at each subsequent visit after the first visit (assessed by the number of subjects recording no pain). The incidence of itching was low (only one subject recorded itching at one visit).

ZOMACTON 10 mg was well tolerated in this study and there were no safety concerns.