

## Expert Report on the Clinical Documentation for Genotropin<sup>®</sup> INJEX<sup>™</sup>

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## 1. ABBREVIATIONS, ACRONYMS, AND DEFINITIONS OF TERMS

AUC <sub>0-∞</sub> :	area under the serum concentration-time curve from time zero to infinity
AUC <sub>0-∞</sub> FDA:	area under the serum concentration-time curve from time zero to infinity calculated by a linear mixed model as requested by FDA
AUC <sub>0-last</sub> :	area under the serum concentration-time curve from time zero to time of last detectable serum concentration
CE:	Conformité Européene (European Conformity mark)
CI:	confidence interval
C <sub>max</sub> :	maximum observed serum concentration
CPMP:	Committee for Proprietary Medicinal Products
CRF:	case report form
EU:	European Union
FDA:	Food and Drug Administration
GH:	growth hormone
GHD:	growth hormone deficiency
ITT:	intent-to-treat
KIGS:	Pharmacia International Growth Database
NOS:	not otherwise specified
PP:	per protocol
t <sub>max</sub> :	time to maximum observed serum concentration
t <sub>1/2</sub> :	terminal half-life
US:	United States

## 2. PROBLEM STATEMENT

This clinical expert report describes the rationale for the use of a needle-free injection device (INJEX™) for the administration of Genotropin<sup>®</sup> (somatropin or growth hormone [GH]) in order to offer patients and healthcare providers the delivery option of a needle-free method of injection. This report discusses the results from clinical trials performed to support the claim for the use of Genotropin INJEX.

### Rationale for needle-free injection of growth hormone

GH is a glycoprotein secreted by the pituitary gland and is a metabolic hormone important not only for growth, but also for the metabolism of lipids, carbohydrates and proteins. Somatropin, the active ingredient in Genotropin,

is synthetic human GH that has the normal structure of the major (22K) component of natural pituitary GH. The gene for somatotropin has been cloned and expressed in bacterial cells (*Escherichia coli*). Genotropin (somatotropin [recombinant DNA origin] for injection) is identical to endogenous human GH and is indistinguishable on the basis of immunological and functional assays.

Genotropin was first approved in 1987 and is currently indicated for the treatment of growth hormone deficiency (GHD) in both children and adults, as well as growth disturbance associated with Turner syndrome or chronic renal insufficiency, and Prader-Willi syndrome in children.

Treatment with GH involves daily subcutaneous injections, often for several years, which can lead to problems with compliance and patient acceptance [1]. Any potential improvement in the convenience of treatment will help patients cope with the daily administration of GH [2]. In addition to standard single-use syringes, various injection devices are available for GH administration. One of the most common devices is the injection pen, e.g. Genotropin Pen<sup>®</sup>, which is generally well accepted and well tolerated by most patients. However, pen injection systems still use needles, albeit of a small gauge, and this can cause problems for needle-phobic patients and have a negative effect on compliance and treatment outcome. For example, subjects with Type I diabetes who have phobic symptoms such as increased fear of blood and injury, perform fewer blood glucose measurements and have poorer glycemic control than those without fear of blood/injury [3].

Needle injections can be painful and sometimes fear-provoking for children [4]. These injections are either administered by the children themselves or with the help of their parents/guardian and there have been reports of negative effects on child-parent relationships as a result of pain, fear and aversion to needles [5, 6]. Problems associated with the dislike of repeated subcutaneous needle injections can be overcome by the use of needle-free jet injectors [7] and patients are likely to be less apprehensive because no needle is involved [8].

Needle-free injectors were initially developed for mass immunization programs. More recently, they have been used for insulin administration in diabetic subjects as an alternative to subcutaneous injection or pump delivery [9]. Needle-free delivery has no major effect on plasma insulin profiles compared with conventional syringe injection, and it has been reported that the rate of insulin absorption and free insulin levels are increased following needle-free injection [9, 10, 11]. Surveys have also indicated a degree of patient preference for needle-free devices [12], particularly following recent improvements in device design [7]. The use of needle-free devices has

expanded to other therapeutic areas including delivery of heparin and pain medication [8], sedatives [13], and induction of local anesthesia [14].

A number of needle-free injection devices are now also available for the administration of different marketed formulations of GH [15, 16, 17]. Pharmacia have selected the INJEX device in order to offer patients and healthcare providers the delivery option of a needle-free method of injection for GH patients who use Genotropin.

### **INJEX device**

The INJEX device from Rösch AG, Medizintechnik, Berlin, Germany, is a reusable needle-free device that has advantages for those subjects with a dislike or phobia for needles, as well as offering a new Genotropin injection device choice to patients and healthcare providers. The INJEX device utilizes a spring mechanism to propel drug solution through a micro-orifice (0.17 mm) under high pressure. The microjet stream of drug solution traverses the skin and the drug disperses into subcutaneous adipose tissue to a depth of 3 to 9 mm.

The INJEX device received the Conformité Européene (CE, European Conformity) mark approval in September 1999 for subcutaneous administration of drugs (as required by the European Community medical device directive, 93/42/EEC), and has been marketed in Germany since January 2000.

Genotropin INJEX represents a new addition to the line of Genotropin injection devices. The Sponsor intends to offer patients and healthcare providers the delivery option of a needle-free method of injection for patients who currently receive Genotropin therapy for any approved indication either by pen injection or conventional syringe.

The Sponsor does not propose to change the recommended dosages of Genotropin. Subjects who switch to the INJEX device will be advised to continue to administer their current dose of Genotropin.

### **3. COMPLIANCE WITH GOOD CLINICAL PRACTICES**

All studies fully adhered to the Good Clinical Practices (GCP) guidelines of the Committee for Proprietary Medicinal Products (CPMP) and Directive 91/507/EEC of the European Union (EU). In addition, all studies were compliant with the European Standard EN540 Clinical Investigation of Medical Devices for Human Subjects [18].

All studies were closely monitored by Pharmacia personnel or a contract organization for compliance to the protocol and the procedures described in it. Studies were conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

## **4. CLINICAL PHARMACOLOGY**

### **4.1. Performance Testing of the INJEX Device**

Performance tests conducted with the INJEX device examined the effects of needle-free jet injection on the structure of administered compounds, the depth of tissue penetration and the histology of tissue surrounding the injection site. A shear study examining the effects of injecting Genotropin (36 IU, 12 mg/mL) via the INJEX device showed only marginal effects on the chemical quality of Genotropin with a small decrease in monomers and a small increase in dimers and polymers. A low injection volume (0.1 mL) appeared to have a lesser effect than a higher volume (0.3 mL) [19]. None of these effects are thought to have any relevance.

Radiography of the triceps area of a healthy volunteer showed that penetration of radio-dense saline solution after injection by INJEX was strictly limited to the subcutaneous tissue [20]. An ex-vivo study has also demonstrated the tissue-preserving properties of INJEX needle-free injection: a deposit cone was observed in the subcutaneous fatty tissue under a fully intact epidermis without any remarkable edema formation [21]. A preclinical dye-injection study has shown that jet-injected fluids tend to follow the path of least resistance and show a noticeable subcutaneous spread, but do not penetrate bone, the media of blood vessels or nerve fibers [22].

### **4.2. Pharmacokinetics**

#### **4.2.1. Pharmacokinetics in Healthy Volunteers**

The pharmacokinetics of GH were determined in healthy volunteers in Study PHA-GENAIN-0539-001 (formerly coded PHA-307-MET-0539-001) after the administration of Genotropin by the INJEX device or conventional syringe.

This was an open-label, randomized, replicate design, four period, crossover study performed in 18 healthy male (N=14) and female (N=4) adult subjects. Subjects received subcutaneous injections of 3.6 mg Genotropin (0.30 mL of Genotropin 12 mg/mL) administered either using the INJEX needle-free device or a conventional syringe (Becton-Dickinson 0.33 x 12.7 mm, 0.50 mL

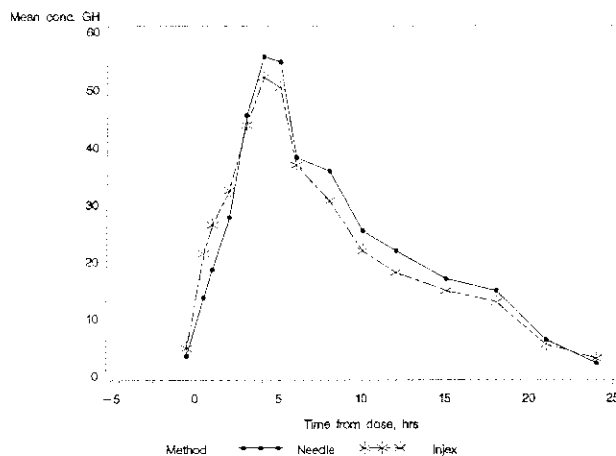
insulin syringe). In order to ensure consistency in drug administration, the same research nurse carried out all injections in each subject.

The primary objective of the study was to show bioequivalence with respect to area under the serum concentration-time curve from time zero to infinity ( $AUC_{0-\infty}$ ) when Genotropin (GH) was administered by INJEX device and conventional subcutaneous injection. An analysis of variance was performed where  $AUC_{0-\infty}$  after log-transformation was described by a linear model. Bioequivalence was declared with respect to log-transformed  $AUC_{0-\infty}$  when the 90% CI of the treatment ratio was contained within the equivalence range of 80% to 125% [23].

New guidance from the United States (US) Food and Drug Administration (FDA) states that in replicated, crossover design studies, linear mixed model procedures should be used to establish bioequivalence [24], in addition to the fixed model specified in the protocol for this study. Therefore, an additional variable ( $AUC_{0-\infty}$  FDA) based on the mixed model was also used to confirm bioequivalence, since the Sponsor plans to submit the Genotropin INJEX dossier in the US as well as the EU.

Figure 1 shows that mean GH serum concentration-time profiles were similar after administration of Genotropin by either the INJEX device or conventional syringe.

**Figure 1. Mean GH Concentration-time Profiles after Administration of Genotropin via the INJEX device or Conventional Syringe**



Source: PHA-GENAIN-0539-001 study report

The descriptive statistics for the pharmacokinetic parameters of GH in Study PHA-GENAIN-0539-001 are shown in Table 1. The pharmacokinetics of GH were similar after administration of Genotropin using the INJEX device or conventional syringe.

**Table 1. Pharmacokinetic Parameters of GH in Healthy Volunteers**

Parameter	INJEX (N=17)	Conventional Syringe (N=17)
<b>C<sub>max</sub> (mU/L)</b>		
Median (range)	56.4 (25.2–135)	57.1 (25.2–160)
Mean ± SD	57.9 ± 22.4	64.3 ± 26.0
<b>t<sub>max</sub> (h)</b>		
Median (range)	4.00 (1.00–15.0)	5.00 (3.00–18.0)
Mean ± SD	4.73 ± 2.24	6.00 ± 3.68
<b>AUC<sub>0-∞</sub> (mU/L x h)</b>		
Median (range)	528 (398–878)	557 (320–847)
Mean ± SD	549 ± 124	553 ± 107
<b>AUC<sub>0-last</sub> (mU/L x h)</b>		
Median (range)	511 (361–877)	553 (312–835)
Mean ± SD	530 ± 129	541 ± 111
<b>t<sub>1/2</sub> (h)</b>		
Median (range)	3.07 (1.49–6.80)	2.78 (1.44–6.18)
Mean ± SD	3.68 ± 1.68	2.92 ± 1.05

SD = standard deviation  
Source: PHA-GENAIN-0539-001 study report

The relative bioavailabilities of log-transformed AUC<sub>0-∞</sub> and C<sub>max</sub> for GH administered with the INJEX device or conventional syringe are shown in Table 2.

**Table 2. Relative Bioavailability of GH Administered using the INJEX Device and Conventional Syringe**

Parameter	Ratio of Geometric means INJEX : Conventional syringe	90% CI (lower bound)	90% CI (upper bound)
AUC <sub>0-∞</sub>	0.99	0.94	1.04
C <sub>max</sub>	0.92	0.82	1.04
AUC <sub>0-∞</sub> FDA	0.99	0.94	1.05
C <sub>max</sub> FDA	0.91	0.76	1.10

CI = confidence interval  
Source: PHA-GENAIN-0539-001 study report

The 90% CI of the treatment ratio for log-transformed AUC<sub>0-∞</sub> (and also AUC<sub>0-∞</sub> FDA) of GH administered using the INJEX or conventional syringe was contained within the equivalence range of 80% to 125%. Therefore, it can be concluded that Genotropin administered using the INJEX needle-free device is bioequivalent to Genotropin administered by conventional subcutaneous injection.

#### 4.2.2. Pharmacokinetics in Patients

No pharmacokinetic investigations with Genotropin INJEX were performed in children as the Sponsor felt it would be unethical to submit children to the rigorous blood sampling involved in such a study. However, a study using another jet injector device has shown similar GH pharmacokinetics for human recombinant GH given by needle-free or needle injection in GH-deficient children and adolescents [25]. As bioequivalence for Genotropin administered by the INJEX device compared with a conventional syringe was confirmed in healthy adult subjects (as required by the CPMP [23]), pharmacokinetic studies with Genotropin INJEX were not warranted in patient populations.

#### 4.3. Clinical Pharmacology Conclusions

The data show that the pharmacokinetics of GH are similar after administration of Genotropin via the INJEX needle-free device or a conventional syringe. Furthermore, bioequivalence was confirmed between the two administration methods as the 90% CI of the treatment ratio for log-transformed  $AUC_{0-\infty}$  of GH was within the equivalence range of 80% to 125%. Therefore, it can be concluded that Genotropin administered using the INJEX needle-free device is bioequivalent to Genotropin administered by conventional subcutaneous injection.

### 5. CLINICAL STUDIES

#### 5.1. Overview of the Clinical Program

As a result of the extensive clinical experience already available with Genotropin, together with the CE-mark of approval for subcutaneous drug administration with the INJEX device, it was deemed unnecessary to conduct a full clinical program for Genotropin INJEX.

Genotropin was first approved in Europe in 1987 and according to European regulatory requirements, an abridged application is permitted when the medicinal product is essentially similar to a product that has been authorized for not less than 6 or 10 years. The Genotropin formulation for use with the INJEX device is identical to that currently available. As Genotropin administered using the INJEX device is bioequivalent to Genotropin administered by conventional subcutaneous injection, the Sponsor felt that demonstration that there were no safety issues associated with the use of the INJEX device would be sufficient. Therefore, no clinical efficacy trials were performed; confirmation of this decision was discussed in writing with Lægemiddelstyrelsen (The Danish Medicines Agency) on February 21, 2001.

In addition to the bioequivalence study described in Section 4.2.1, the Genotropin INJEX clinical program consists of one Phase 3 study (PHA-GENAIN-0539-003) that compared the safety of the INJEX device to a needle injection device for the administration of Genotropin (see Section 5.3. for further details). Following advice from the Danish Medicines Agency (Lægemiddelstyrelsen), the Sponsor chose a crossover design with a control group treated by conventional subcutaneous injection.

The safety study was conducted in a pediatric patient cohort. There is currently limited information regarding the use of the INJEX device in this important target population. However, a study by Sarno *et al.* has shown that the measles, mumps and rubella vaccine can be safely and effectively delivered to children (aged 9 to 14 years) by the INJEX injector [26]. The Sponsor feels that any safety findings associated with the use of the INJEX device in pediatric patients can be extrapolated to adult patients.

Appendices 1 and 2 contain the tabular summaries of the clinical studies in the Genotropin INJEX submission.

## 5.2. Dose-Selection Studies

Dose-selection studies were not required as the dosage and administration schedule for Genotropin should be individualized. In addition, any subject switching to the INJEX device would be advised to continue with their existing dose of Genotropin.

## 5.3. Assessment of Individual Studies

Study PHA-GENAIN-0539-003 was a multi-center, randomized, two-period crossover study (2 + 2 weeks) that compared the safety of the INJEX needle-free device to a needle injection device for the administration of Genotropin to pediatric patients with GHD who were currently using Genotropin. As the study duration was only for a 4-week period, spontaneous change in the patient's growth during this time was not anticipated and for this reason no efficacy assessments were made.

The study was performed at six sites (one in the Netherlands and five in Germany) and patients who met the following key criteria were eligible for inclusion:

- Age  $\geq 6$  years diagnosed with GHD
- Received regular injections of GH for more than 3 months
- Weighed  $\geq 18$  kg

Patients were excluded if they had previous experience of a needle-free device in order to ensure an objective evaluation of the INJEX device. In addition, as injection site bleeding was a response variable, any patients with a known bleeding disorder, or who had used aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) within 7 days of the first study visit, or heparin or warfarin within 28 days of the first study visit, were also excluded. Genotropin was administered once daily either by the patient themselves or their parent/guardian. The dose of Genotropin varied between patients according to their requirements.

Safety was assessed by the incidence of bleeding at the injection site, adverse events, and physical examination of the injection sites. In addition, injection site pain, soreness and bruising were also recorded. Pain was recorded at the time of injection only, and soreness and bleeding were recorded immediately after the device was removed and again at 10 and 30 minutes after injection. Bruising was recorded 24 hours after the previous injection and before injecting the next dose.

At the end of the study, patients were asked whether they preferred the INJEX device or needle-injection device. All patients were also offered the opportunity to continue treatment with the INJEX device at the end of the study.

The primary objective of the study was to determine whether the INJEX device was at least as safe as a needle device over a 2-week treatment period. The primary analysis was based on data recorded from week 2 of each treatment period. The primary response variable was the incidence of injection site bleeding. Symptoms (bleeding, injection site pain, soreness and bruising) associated with the use of the INJEX device or the patient's own needle device were collected on a daily diary card, using a verbal rating scale where: None=0, Mild=1, Moderate=2, Severe=3.

### 5.3.1. Statistical Analysis

The objective of the study was to demonstrate the non-inferiority of INJEX compared to the patient's usual needle injection device. Non-inferiority was defined as a difference in incidence rates of 10 percentage points. The sample size calculation was based on a treatment comparison of 55% with no injection site bleeding on needle vs. 45% on INJEX (since this maximized the sample size, and ensured the desired power of the study). This corresponded to an odds ratio (needle to INJEX) of 1.49 (i.e. the odds of no injection site bleeding on needle must be less than 1.5 times the odds of no injection site bleeding on INJEX for a claim of non-inferiority to be made). A conservative approach to claiming non-inferiority of INJEX compared to the patient's own

needle device required that the upper 95% confidence limit for the odds ratio did not exceed 1.49 (i.e. the CI does not include a value that is consistent with inferiority).

## **6. GLOBAL ANALYSIS OF EFFICACY**

No efficacy data were recorded in the Genotropin INJEX clinical program. However, the efficacy of Genotropin is well established in GH-deficient children, in prepubertal children with chronic renal insufficiency, in girls with Turner syndrome and in GH-deficient adults.

Since bioequivalence was confirmed with regards to the GH AUC<sub>0-∞</sub> ratio of INJEX to conventional subcutaneous injection (see Section 4.2.1), it can be assumed that the clinical efficacy of Genotropin administered by the two injection systems would also be equivalent.

## **7. GLOBAL ANALYSIS OF SAFETY**

### **7.1. Classification of Studies**

The main focus of the safety investigations was the safety of the INJEX device compared with that of needle injection in GH-deficient children in the Phase 3 Study PHA-GENAIN-0539-003. Safety results (adverse event and laboratory safety data) from the Phase 1 bioequivalence Study PHA-GENAIN-0539-001 in healthy adult volunteers are summarized briefly.

### **7.2. Extent of Exposure in PHA-GENAIN-0539-003**

A total of 133 patients received at least one dose of Genotropin delivered using the allocated device. Daily doses ranged from 0.40 mg to 2.40 mg.

### **7.3. Demographic Characteristics in PHA-GENAIN-0539-003**

Of the 134 patients randomized to treatment, 133 received treatment with their allocated device and were included in the intent-to-treat (ITT) cohort. The ITT cohort consisted of all patients who took at least one dose of study medication. An evaluable cohort (per protocol, PP) consisted of all patients in the ITT cohort who provided diary card data from the second week of both treatment periods and were not considered to be major protocol violators. A total of 117 patients were included in the PP cohort; of these, 57 were randomized to the INJEX-needle treatment sequence and 60 were randomized to needle-INJEX.

Safety analyses were carried out for both of these cohorts. However, analyses based on the PP cohort were regarded as primary for the assessment of non-

inferiority of INJEX relative to needle injection and are described in this expert report.

Details of the main demographic characteristics of the PP cohort are summarized in Table 3. The two treatment groups were well matched for demographic characteristics.

**Table 3. Demographic Characteristics (PP Cohort)**

Demographic variable	INJEX-needle (N=57)	Needle-INJEX (N=60)
Sex N (%)		
Male	35 (61.4)	41 (68.3)
Female	22 (38.6)	19 (31.7)
Race N (%)		
White	57 (100)	58 (96.7)
Black	0	1 (1.7)
Not listed	0	1 (1.7)
Age (years)		
Mean (SD)	11.5 (2.76)	11.0 (2.88)
Median (range)	12.0 (5-16)	11.0 (6-17)
Age category (years), N (%)		
Under 10	17 (29.8)	16 (26.7)
10-19	40 (70.2)	44 (73.3)
Weight (kg)		
Mean (SD)	40.0 (18.73)	37.3 (15.59)
Median (range)	36.2 (17-103)	36.3 (12-91)

SD = standard deviation

Source: PHA-GENAIN-0539-003 study report

Both treatment groups had similar exposure profiles to GH, in terms of mean treatment duration, usual daily dose and frequency of injections.

Approximately 50% of injections in both treatment groups were administered by the child alone. The majority of patients (112/117, 95.7%) used the Genotropin Pen, which is considered the current "gold-standard" injection device in terms of ease of use and comfort/safety for the administration of Genotropin, as their most recent device. The needle gauges available for the Genotropin Pen were 29, 30 or 31G in Germany and 31G in the Netherlands, thus all patients using the pen took advantage of a very fine needle.

#### 7.4. Treatment Discontinuations in PHA-GENAIN-0539-003

No patients in the PP cohort prematurely discontinued treatment. However, by definition, patients in the PP cohort had to provide diary card data from the second week of both treatment periods. Five patients in the ITT cohort (5/133, 3.8%) prematurely discontinued treatment. Details of the two patients who discontinued due to an adverse event are provided in Section 7.6.1.

### 7.5. Injection Site Symptoms in PHA-GENAIN-0539-003

PP analyses were based on those patients who provided diary card data from the second week of each treatment period. This section focuses on the incidence of injection site bleeding which was the primary response variable. The results for symptoms of pain, bruising and soreness were similar to those for bleeding and non-inferiority was not met. Details of these symptoms are given in the PHA-GENAIN-0539-003 study report.

Three response variables were derived from the individual diary card pages in order to provide a detailed characterization of each symptom's profile. The derived variables were:

- Absence/presence of symptom during the week
- Average symptom score during the week
- Maximum symptom score during the week

These three response variables were derived for each week, and for each time-point relative to the time of the injection (at the time of the injection, 10 minutes after injection and 30 minutes after injection).

For each patient, the symptom response while using the INJEX device was compared to the symptom response with the needle device. Details of the patient assessment of absence/presence of injection site bleeding are shown in Table 4.

**Table 4. Patient Assessment of Injection Devices for the Absence/Presence of Injection Site Bleeding (PP Cohort, N=117)**

	Better on INJEX		Same		Better on Needle	
	N	%	N	%	N	%
<b>Week 1</b>						
At time of injection	2	1.7	75	64.1	40	34.2
10 minutes after	8	6.8	77	65.8	32	27.4
30 minutes after	3	2.6	107	91.5	7	6.0
<b>Week 2</b>						
At time of injection	9	7.8	72	62.1	35	30.2
10 minutes after	5	4.3	86	74.1	25	21.6
30 minutes after	3	2.6	105	90.5	8	6.9

Source: PHA-GENAIN-0539-003 study report

At week 2, the majority of patients considered the bleeding response at each timepoint after injection to be the same with both injection devices. The injection site bleeding responses at week 1 showed a similar profile to that of week 2.

At week 2, the upper 95% confidence limits for the analysis of injection site bleeding (odds ratio, needle to INJEX, for presence/absence of symptoms) at the time of injection, 10 minutes after injection and 30 minutes after injection were 4.39, 6.59 and 5.48, respectively. At week 1, the corresponding upper 95% confidence limits were 16.27, 6.16 and 5.87, respectively. Therefore, the results did not support the hypothesis of non-inferiority of INJEX to the needle device (defined as an upper 95% confidence limit for the odds ratio not exceeding 1.49). It became apparent that the incidence of injection site symptoms was numerically greater on INJEX than on a needle device. A post-hoc decision was taken to perform a two-sided test for a difference between the devices, which showed that INJEX was statistically inferior to the needle device ( $p < 0.001$  at week 2).

Similar findings were observed for patient assessment of average bleeding severity and maximum bleeding severity, in that the majority of patients considered the response as the same between devices or better with the needle device. Over the course of week 2, 53/117 (45.3%) patients considered the average bleeding severity with INJEX to be mild at the time of injection compared with 12/116 (10.3%) patients with the needle device. In addition, 3/117 (2.6%) patients considered the average bleeding severity with INJEX to be moderate compared with no patients with the needle device. All other patients considered the average bleeding severity at the time of injection as None.

Overall, the results of injection site bleeding did not support the hypothesis of non-inferiority of INJEX to the needle device. Moreover, a two-sided comparison showed that INJEX was statistically inferior to the needle device. However, it should be noted that the patient population in this Phase 3 study were not needle-phobic and were comfortable with the use of the Genotropin pen or other needle device. It may therefore not be that surprising that subjects felt injection site symptoms were better with their usual needle device. In addition, more than 50% thought that injection by either needle or INJEX were the same, demonstrating acceptable tolerability of the needle-free device. The Sponsor felt it unethical to use a needle-phobic population in the study as they would have had to use a needle injection device for a 2-week period.

## 7.6. Adverse Events

### 7.6.1. Adverse Events in PHA-GENAIN-0539-003

Adverse event data were generated for both the PP and ITT cohorts. However, only data for the ITT population, which included all patients who received at least one dose of study medication, are shown here.

Adverse events reported in at least 1% of patients in either treatment group are shown in Table 5.

**Table 5. Adverse Events Reported in  $\geq 1\%$  of Patients in Either Treatment Group (ITT Cohort)**

Adverse event preferred term	Number (%) of patients	
	INJEX	Needle
Patients for whom data were reported <sup>a</sup>	132 (100.0)	130 (100.0)
Patients with at least one adverse event	29 (22.0)	17 (13.1)
Arthropod sting	1 (0.8)	2 (1.5)
Bronchitis NOS	2 (1.5)	0 (0.0)
Device failure NOS	13 (9.8)	2 (1.5)
Fall	0 (0.0)	2 (1.5)
Headache NOS	1 (0.8)	2 (1.5)
Nasopharyngitis	2 (1.5)	0 (0.0)
Sore throat NOS	2 (1.5)	0 (0.0)

<sup>a</sup> Both treatment periods combined. The table includes patients who used both devices. It excludes patients who withdrew during Period 1.

NOS = not otherwise specified

Patients may appear more than once if they experienced more than one adverse event

Source: PHA-GENAIN-0539-003 study report

The frequency of adverse events was low with both the INJEX (22.0%) and needle devices (13.1%). Exclusion of device failure not otherwise specified (NOS) (verbatim term: wet shots, clear liquid spilling out of injection hole) from the adverse event data showed that the overall frequency of adverse events was similar for the INJEX (20/132 patients, 15.2%) and needle devices (16/130 patients, 12.3%).

The majority of adverse events were of mild or moderate intensity. No deaths or serious adverse events were reported. Two patients discontinued study medication due an adverse event: one patient due to an event of nervousness during the INJEX treatment period and one patient due to adverse events of nervousness, abdominal pain NOS, vomiting NOS and pyrexia during the needle device treatment period.

#### 7.6.1.1. Device-Related Treatment-Emergent Adverse Events

In the analysis of adverse event data, the term "related to drug" was used to classify the relationship between adverse event and both the Genotropin administered **and** the device (INJEX or needle) used to administer the drug. Although investigators were made aware they should be recording both device-related and investigational-drug related adverse events, the adverse event page of the case report form (CRF) only gave the option of assigning whether an adverse event was related to the investigational drug or the disease: there was no specific option for designating whether an adverse event was related to the injection device. Therefore, the data captured may not be a

true representation of the causal relationship between adverse events and the devices used.

Six patients reported six adverse events (one event per patient) that were considered related to the study drug/device. Five patients had the event with the INJEX device and one patient with the needle device. All of the events considered related to the drug/device were either of mild or moderate intensity. No adverse events related to the disease were reported during the study.

#### **7.6.1.2. Adverse Events of Device Failure**

Any adverse events associated with the use of the injection devices were of interest in the study. As shown in Table 5, the most frequently reported adverse event was device failure NOS (wet shots, clear liquid spilling out of injection hole), which involved the appearance of clear fluid at the injection site after administration of study medication. Only two of the 16 device failure events were considered related to the drug/device, although this may not be truly representative due to the reasons given in Section 7.6.1.1 concerning the absence of the option on the CRF for investigators to assign a causal relationship between event and device.

Although the majority of device failure events occurred with INJEX, this may be associated with the injection technique and/or relative inexperience of the patient (or their parent/guardian) in using INJEX compared with their current needle-injection device, rather than failure of the device itself. At entry into the study, patients were to have been using their current injection device for at least three months, whereas they only had a short time to become familiar with INJEX. Similar injection failures (i.e., wet shots, wet injections) have been reported with other needle-free injection devices [7, 17], and have also been reported in diabetic children using a conventional syringe to administer insulin [27].

#### **7.6.2. Adverse Events in PHA-GENAIN-0539-001 (Bioequivalence Study)**

Thirteen out of 18 subjects reported a total of 23 adverse events. The most common events were headache (total of eight events reported by five subjects) and rhinitis (six events reported by six subjects). All adverse events were of mild or moderate intensity and none were considered related to the study drug or devices. One subject discontinued due to an adverse event of thrombophlebitis caused by the blood sampling cannula after the second treatment period. The subject had fully recovered at the follow-up visit. No subjects died in the study and no serious adverse events were reported.

### 7.7. Laboratory Assays

Since the main safety evaluations were concerned with the use of the INJEX or needle device and not the effects of Genotropin *per se*, no laboratory safety assessments were performed in PHA-GENAIN-0539-003.

In PHA-GENAIN-0539-001, laboratory tests were performed at screening and approximately 24 hours after the final administration of study medication. These tests were performed primarily to monitor subject health and were not collected to correspond with maximum plasma concentrations of Genotropin. No abnormal laboratory values of clinical relevance were observed.

### 7.8. Vital Signs

In PHA-GENAIN-0539-003, weight, height, body mass index, systolic and diastolic blood pressure, pulse rate and body temperature were recorded for each treatment group at baseline, and the end of treatment Periods 1 and 2. There were no statistically significant differences in the mean values of any parameter between treatment groups at each timepoint. Within each treatment group, there was no clinically relevant change from baseline in the mean values of any vital sign.

In PHA-GENAIN-0539-001, vital signs (weight, height, heart rate and supine blood pressure) were only performed at screening.

### 7.9. Electrocardiograms

As for laboratory assays, the focus of the safety evaluations was related to the use of the injection devices, and therefore no electrocardiograms were performed in the Genotropin INJEX studies.

### 7.10. Other Analyses

In the PP cohort in PHA-GENAIN-0539-003, 26/117 patients (22.2%) preferred the INJEX device. Of the 112 patients who used the Genotropin Pen as their usual device, 24 (21.4%) preferred INJEX.

Of note is that in a patient population who were not needle-phobic and currently using a pen device with a very fine gauge needle, and despite being unable to establish non-inferiority of the INJEX device for injection site symptoms, approximately 20% of patients decided to continue on the INJEX device instead of their usual needle device at the end of the study; these patients are being monitored on the KIGS database (Pharmacia International Growth Database) and no information is included on them in this report.

### **7.11. Special Patient Populations**

Other than the pediatric population in PHA-GENAIN-0539-003, no special patient populations were assessed in the Genotropin INJEX clinical program. However, any relevant safety information for such subjects described in the current labeling for Genotropin will apply to subjects who use Genotropin INJEX.

### **7.12. Safety Conclusions**

Overall, the needle injection devices performed better in this pediatric age population of patients already comfortable with needle injection. The majority of patients in this trial found INJEX to be the same as needle in terms of the major parameters of bleeding, pain, soreness and bruising. Both the INJEX and needle devices were well tolerated, with a low incidence of adverse events reported for each device. There were no deaths or serious adverse events and only two injection site reactions were reported as adverse events (one with INJEX and one with a needle device). The incidence of device failure adverse events was higher with INJEX, although this may have been due to the patient's relative inexperience of using the INJEX device compared with their usual needle device. In clinical practice, it would be recommended that a patient not switch to INJEX until they (or their parent/guardian) were familiar and comfortable with using the device and had received adequate training during clinic visits.

## **8. POSTMARKETING EXPERIENCE**

There is no postmarketing experience with Genotropin used in conjunction with the INJEX device.

The INJEX device received CE mark approval in September 1999 for subcutaneous administration of drugs and has been marketed in Germany since January 2000. According to Rösch AG, there are approximately 4,000-5,000 patients in Germany who are on long-term treatment utilizing the INJEX system, predominantly to deliver insulin.

## **9. OTHER INFORMATION**

### **9.1. Prematurely Discontinued Studies**

No studies with Genotropin INJEX have been prematurely discontinued.

### **9.2. Ongoing Studies**

There are no ongoing studies with Genotropin INJEX.

## 10. BENEFIT-RISK ASSESSMENT AND CONCLUSIONS

The rationale behind the development of Genotropin INJEX is to offer patients and healthcare providers the option of a needle-free method of injection for patients who currently receive Genotropin therapy for any approved indication either by pen injection or conventional syringe.

The data presented in this expert report show the pharmacokinetics of GH are similar after administration of Genotropin via the INJEX needle-free device or a conventional syringe. Furthermore, bioequivalence of GH was confirmed between the two administration methods. Therefore, it can be concluded that Genotropin administered using the INJEX needle-free device is bioequivalent to Genotropin administered by conventional subcutaneous injection. It is therefore likely that the clinical efficacy of Genotropin would also be equivalent whether administered via INJEX or a needle device.

In a target population of GH-deficient children, non-inferiority of INJEX compared to a needle device for the administration of Genotropin could not be established statistically for assessment of injection site symptoms (bleeding, pain, soreness and bruising). In addition, there was evidence to show that INJEX was statistically inferior to the patient's current needle device. However, these findings need to be placed in context with regards to the device experience and characteristics of the patient population. Patients were not needle-phobic and were skilled in using their current needle device. The majority of patients used the Genotropin pen, which uses a fine gauge needle and is the current "gold standard" device for administration of Genotropin in terms of comfort and safety, as their usual device. By selecting such patients, the Sponsor set a very stringent test for Genotropin INJEX and these factors probably contributed to the better injection site response overall with the needle device. Nevertheless, approximately 20% of patients still preferred to switch to Genotropin INJEX at the end of the study; these patients are being monitored in the KIGS database.

Both the INJEX and needle devices were well tolerated, with a low incidence of adverse events reported for each device. Although the incidence of device failure adverse events was higher with INJEX, this may have been due to the patient's relative inexperience of using the INJEX device compared with their usual needle device. In clinical practice, it is recommended that a patient would not switch to INJEX until they (or their parent/guardian) were familiar with the injection technique and comfortable with using the device.

One of the potential benefits of the INJEX device is that it obviates the risk of needle-stick injuries [26] and may help eliminate the possibility of cross-contamination, e.g. from parent/guardian to child. In addition, it has been claimed that needle-free GH administration tends to lead to fewer adverse

psychological responses than a multidose injection pen [16], which may be of benefit to those patients unable, unwilling or who have no desire to use needles to administer GH.

No safety issues were observed that prohibit the use of the INJEX device in children. The Sponsor proposes that Genotropin INJEX should be approved for the same indications as currently available for Genotropin administered via conventional syringe or needle device. The dosage and administration schedule of Genotropin should be individualized and patients who choose to switch to the INJEX device will be advised to continue using their current dose of Genotropin.

The pharmacokinetic and safety data from the clinical program indicate that Genotropin INJEX should not have an altered efficacy and safety profile compared to Genotropin administered via needle injection. Genotropin INJEX should continue to provide the known therapeutic benefits of Genotropin injected via conventional needle methods. The option of needle-free delivery may lead to patient acceptance in those patients requiring Genotropin therapy and who have needle phobia or a preference for needle-free injection.

## 11. INFORMATION ON THE CLINICAL EXPERT

**Name:** Steven L. Schoenfeld

**Education:**

M.D.- 1983. New York Medical College

B.S. in Biomedical Sciences- 1981, City College of New York School of Biomedical Education (combined, joint BS/MD Program)

**Publications:** 48 Abstracts, 6 peer-reviewed publications relating to metabolic and bone diseases and 1 book chapter on pharmacokinetics of antisense compounds.

**Appointments:**

Vice Chairman, Passaic Township Board of Health, New Jersey 1992-1993

Member, Passaic Township Board of Health, New Jersey 1991-1992

Provisional Medical Staff, Emergency Department, St. Cabrini Hospital of Seattle, 1988

Representative, Executive Committee/Medical Board, Westchester County Medical Center, 1985-1986

Representative, Medical Board Sub-Committee on Medical Practice, 1985-1986

President, Westchester County Medical Center, Committee of Interns and Residents,  
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**Training:**

Senior Research Fellow, Diabetes Endocrinology Research Center, Department of  
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Senior Director, CV/Metabolic Diseases, Pharmacia Ltd., June 2000- Present

Director, Drug Development, Isis Pharmaceuticals, Inc., January 1999- June 2000

Senior Director, Clinical Development, Amylin Pharmaceuticals, Inc., January 1996-  
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Full time employee as of June 2000

## 12. REFERENCES

1. Smith SL, Hindmarsh PC, Brook CGD. Compliance with growth hormone treatment – are they getting it? *Arch Dis Child* 1993;68:91-3.
2. Jørgensen JT. Improvement of patient convenience in treatment with growth hormone. *J Pediatr Endocrinol* 1994;7:175-80.
3. Berlin I, Bisserbe JC, Eiber R, Balssa N, Sachon C, Bosquet F, *et al.* Phobic symptoms, particularly the fear of blood and injury, are associated with poor glycemic control in Type I diabetic adults. *Diabetes Care* 1997;20:176-8.
4. Fassler D. The fear of needles in children. *Am J Orthopsychiatry* 1985;55:371-7.
5. Theintz GE, Sizonenko PC. Risks of jet injection of insulin in children. *Eur J Pediatr* 1991;150:554-6.
6. Sjoblom K, Albertsson-Wikland K, Bengtsson BA, Johannsson G, Thoren M, Degerblad M, *et al.* Patient evaluation of a new injection pen for growth hormone treatment in children and adults. *Acta Paediatr Suppl* 1995;411:63-5.
7. Gonzalez JL, Verrips GH, Fekkes M, Hirasing RA, Groth M. Psychological responses to the needle-free injection of insulin with the disposable front-end Medi-Jector<sup>®</sup> (MJ-6). *Today's Ther Trends* 1998;16:53-71.
8. Baer CL, Bennett WM, Folwick DA, Erickson RS. Effectiveness of a jet injection system in administering morphine and heparin to healthy adults. *Am J Crit Care* 1996;5:42-8.
9. Pehling GB, Gerich JE. Comparison of plasma insulin profiles after subcutaneous administration of insulin by jet spray and conventional needle injection in patients with insulin-dependent diabetes mellitus. *Mayo Clin Proc* 1984;59:751-4.
10. Hallé JP, Lambert J, Lindmayer I, Menassa K, Coutu F, Moghrabi A, *et al.* Twice-daily mixed regular and NPH insulin injections with new jet injector versus conventional syringes: pharmacokinetics of insulin absorption. *Diabetes Care* 1986;9:279-82.

11. Malone JJ, Lowitt S, Grove NP, Shah SC. Comparison of insulin levels after injection by jet stream and disposable insulin syringe. *Diabetes Care* 1986;9:637-40.
12. Denne JR, Andrews KL, Lees DV, Mook W. A survey of patient preference for insulin jet injectors versus needle and syringe. *Diabetes Educ* 1992;18:223-7.
13. Bennett J, Nichols F, Rosenblum M, Condry J. Subcutaneous administration of midazolam: a comparison of the Bioject Jet injector with the conventional syringe and needle. *J Oral Maxillofac Surg* 1998;56:1249-54.
14. Cooper JA, Bromley LM, Baranowski AP, Barker SGE. Evaluation of a needle-free injection system for local anaesthesia prior to venous cannulation. *Anaesthesia* 2000;55:247-50.
15. Bareille P, MacSwiney M, Albanese A, De Vile C, Stanhope R. Growth hormone treatment without a needle using the Preci-Jet 50 transjector. *Arch Dis Child* 1997;76:65-7.
16. Verrips GH, Hirasing RA, Fekkes M, Vogels T, Verloove-Vanhorick SP, Delemarre-Van de Waal HA. Psychological responses to the needle-free Medi-Jector<sup>®</sup> or the multidose Disetronic<sup>®</sup> injection pen in human growth hormone therapy. *Acta Paediatr* 1998;87:154-8.
17. Murray FT, Silverstein JH, Johnson SB, Gertner JH, Frye K, Gironda G, *et al.* Bioequivalence and patient satisfaction with a growth hormone (Saizen<sup>®</sup>) needle-free device – results of clinical and laboratory studies. *Today's Ther Trends* 2000;18:71-86.
18. Clinical investigation of devices for human subjects. European Standard EN 540, 1993.
19. Hyrén C. A shear study for Genotropin 36 IU when injected with the INJEX<sup>™</sup> system, a needle-free device. Pharmacia study PNU-307-MET-0029, February 2001.
20. Gewebeinfiltration nach automatischer Injektion mit INJEX<sup>™</sup> System im Vergleich zu konventioneller Nadeltechnik. Rösch AG Technical Report, August 1999.
21. Bestimmung der histologischen Verteilung eines Farbstoffs und Aufnahme einer Resorptionskinetik von Heparin nach Injektion mit dem INJEX<sup>™</sup>-System. Mediport GmbH, August 2000.

22. Bennett CR, Mundell RD, Monheim LM. Studies on tissue penetration characteristics produced by jet injection. *J Am Dent Assoc* 1971;83:625-9.
23. Note for guidance on the investigation of bioavailability and bioequivalence. CPMP/1401/98, 26 July 2001.
24. Statistical approaches to establishing bioequivalence, US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), January 2001.
25. Houdijk ECAM, Herdes E, Delemarre-Van de Waal HA. Pharmacokinetics and pharmacodynamics of recombinant human growth hormone by subcutaneous jet- or needle-injection in patients with growth hormone deficiency. *Acta Paediatr* 1997;86:1301-7.
26. Sarno MJ, Blase E, Galindo N, Ramirez R, Schirmer CL, Trujillo-Jaurez DF. Clinical immunogenicity of measles, mumps and rubella vaccine delivered by the Injex jet injector: comparison with standard syringe injection. *Pediatr Infect Dis J* 2000;19:839-42.
27. Stewart NL, Darlow BA. Insulin loss at the injection site in children with type 1 diabetes mellitus. *Diabet Med* 1994;11:802-5.

## **APPENDICES**

**Appendix 1. Tabular Summary of Clinical Studies**

**Appendix 2. Individual Tabular Summaries**